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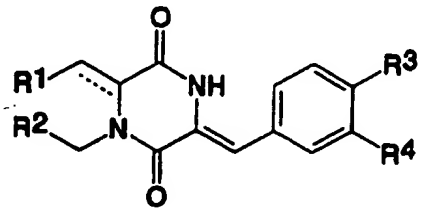
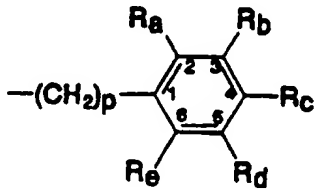
(54) Title: PIPERAZINE 2,5 DIONE DERIVATIVES AS MODULATORS OF MULTI-DRUG RESISTANCE

(57) Abstract

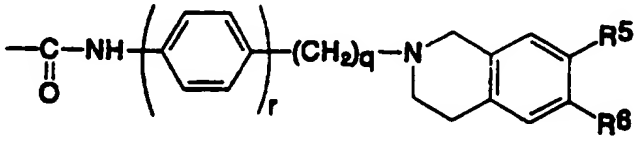
A piperazinedione derivative of formula (I), wherein R^1 is: (i) a group α, wherein p is 0 or 2; (ii) a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from O, N and S, which group may be fused to a benzene ring; R^2 is H, C_1-C_6 alkyl optionally substituted by a group -$N(R^{11}R^{12})$ as defined above, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, -$COOR^{11}$ wherein R^{11} is as defined above or a phenyl ring as defined under (i) above, but is other than H when R^1 is unsubstituted phenyl; and one of R^3 and R^4 is hydrogen and the other is a group of formula (A), wherein q is an integer of 1 to 4, r is 0 or 1 and R^5 and R^6, which may be the same or different, are each H or C_1-C_6 alkoxy, or R^5 and R^6 together form a methylenedioxy group; ---- is a double bond or, when R^1 is as defined under (i) above, is a double bond or a single bond; and pharmaceutically acceptable salts thereof have activity as modulators of multi-drug resistance.



(I)



(i)



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PIPERAZINE 2,5 DIONE DERIVATIVES AS MODULATORS OF MULTI-DRUG RESISTANCE

The present invention relates to compounds useful as modulators of multi-drug resistance (MDR), to their preparation and to pharmaceutical and veterinary compositions containing them.

The resistance of tumours to treatment with certain cytotoxic agents is an obstacle to the successful chemotherapeutic treatment of cancer patients. A tumour may acquire resistance to a cytotoxic agent used in a previous treatment. A tumour may also manifest intrinsic resistance, or cross-resistance, to a cytotoxic agent to which it has not previously been exposed, that agent being unrelated by structure or mechanism of action to any agent used in previous treatments of the tumour.

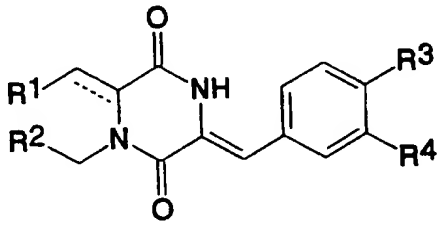
Analogously, certain pathogens may acquire resistance to pharmaceutical agents used in previous treatments of the diseases or disorders to which those pathogens give rise. Pathogens may also manifest intrinsic resistance, or cross resistance, to pharmaceutical agents to which they have not previously been exposed. Examples of this effect include multi-drug resistant forms of malaria, tuberculosis, leishmaniasis and amoebic dysentery.

The above phenomena are referred to collectively as multi-drug resistance (MDR). As discussed more fully later on, a plasma membrane glycoprotein (P-gp) is implicated in the mechanism which underlies MDR. P-gp has drug binding properties. Certain agents which have the capacity to

modulate MDR may therefore also be useful in facilitating the delivery of drugs across the blood brain barrier, and in treating AIDS and AIDS-related complex.

Disadvantages of drugs which have so far been used to modulate MDR, termed resistance modifying agents or RMAs, are that they frequently possess a poor pharmacokinetic profile and/or are toxic at the concentrations required for MDR modulation.

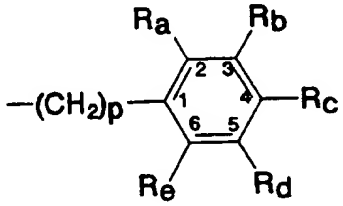
It has now been found that a series of piperazinedione derivatives have activity as modulators of multi-drug resistance. The present invention therefore provides a piperazinedione derivative of formula (I):



(I)

wherein

R_1 is (i) a group



wherein p is 0 or 2;

each of Ra to Re, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy,

nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nCO_2R^{11}$; wherein n is 0 or is an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of Ra and Rb, Rb and Rc, Rc and Rd or Rd and Re together form a methylenedioxy group, or form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted;

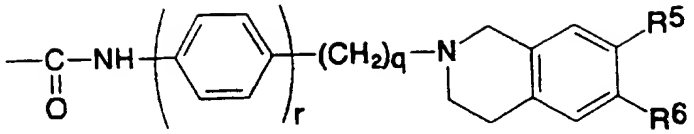
(ii) a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from O, N and S, which group may be fused to a benzene ring;

(iii) a C_1-C_6 alkyl or C_5-C_7 cycloalkyl group; or

(iv) a C_5-C_7 cycloalkenyl group which is unsubstituted or substituted by C_2-C_6 alkenyl;

R^2 is H, C_1-C_6 alkyl optionally substituted by a group $-N(R^{11}R^{12})$ as defined above, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, $-COOR^{11}$ wherein R^{11} is as defined above or a phenyl group as defined under (i) above, but is other than H when R^1 is unsubstituted phenyl; and

one of R^3 and R^4 is hydrogen and the other is a group of formula (A):



(A)

wherein q is an integer of 1 to 4, r is 0 or 1 and R^5 and R^6, which may be the same or different, are each H or C_1-C_6 alkoxy, or R^5 and R^6 together form a methylenedioxy group; and ----- is a double bond or, when R_1 is as defined under (i) above, is a double bond or a single bond; or a pharmaceutically acceptable salt thereof.

A C_1-C_6 alkyl group may be linear or branched. A C_1-C_6 alkyl group is typically a C_1-C_4 alkyl group, for example a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl or tert-butyl group. A C_3-C_6 cycloalkyl group may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A halogen is, for example, fluorine, chlorine, bromine or iodine.

A C_1-C_6 alkoxy group is typically a C_1-C_4 alkoxy group, for example a methoxy, ethoxy, propoxy, i-propoxy, n-butoxy, sec-butoxy or tert-butoxy group. A C_2-C_6 alkenyl group is, for example, C_2-C_4 alkenyl, for example ethenyl, prop-1-enyl or prop-2-enyl.

A heterocyclic group may be, for example, a pyridine, pyrrole, furan or thiophene group which is linked via any one of its constituent ring atoms. It may be, for instance, a 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl group.

The integer q is from 1 to 4, and is preferably 1 or 2.

R^5 and R^6 are preferably the same and are preferably C_1-C_4 alkyl, for instance methyl.

When R^1 is as defined under (i) above, the phenyl group is unsubstituted or is substituted at one or more of positions 2 to 6. When it is mono-substituted it may carry the substituent at any one of positions 2 to 6, for instance position 3 or 4, especially position 4. Thus for instance, one of Ra to Re is other than hydrogen, preferably Rb or Rc, especially Rc. When the phenyl group is mono-substituted the substituent Ra to Re is preferably selected from a halogen, for instance chlorine, bromine or fluorine; a C_1-C_6 alkoxy group, for instance OMe; and an acetamido group -NHAc in which Ac denotes acetyl.

The phenyl group may instead be 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5- disubstituted, or 2,3,4-, 2,3,5-, 2,3,6- or 3,4,5-trisubstituted. When it is disubstituted, three of Ra to Re are hydrogen and two are other than hydrogen. For example Ra and Rb, or Ra and Rc, or Ra and Rd, or Ra and Re, or Rb and Rc, or Rb and Rd are other than hydrogen whilst, in each case, the other three of Ra to Re are hydrogen.

When the phenyl group is trisubstituted, two of Ra to Rc are hydrogen and three are other than hydrogen. For example, Ra, Rb and Rc, or Ra, Rb and Rd, or Ra, Rb and Re, or Rb, Rc and Rd are other than hydrogen whilst, in each case, the other two of Ra to Re are hydrogen.

In a preferred series of compounds of formula (I) each of Ra to Re is hydrogen. In another preferred series of

compounds, one of Ra to Re is selected from hydroxy, C_1-C_6 alkoxy, $NHCOR^{11}$, $-CO_2R^{11}$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, NO_2, $-SO_2N(R^{11}R^{12})$, $-SOR^{13}$, $-N(R^{11})COR^{12}$ and halogen and the other four of Ra to Re are H. Alkoxy may be, for instance, OMe or OBu^n. $NHCOR^{11}$ is typically -NHAc. CO_2R^{11} is typically -COOH or -COOMe. $N(R^{11}R^{12})$ is typically NMe_2. $-CON(R^{11}R^{12})$ may be $-CONH_2$. SO_2R^{13} is typically SO_2Me, $SO_2N(R^{11}R^{12})$ is for example $-SO_2NMe_2$. SOR^{13} may be SOMe and $-N(R^{11})COR^{12}$ may be $-NMeCOBu^t$. Halogen is typically F or Cl. Preferably Rc is alkoxy, especially OMe or OBu^n; $NHCOR^{11}$, especially -NHAc; $-CO_2R^{11}$, especially $-CO_2H$ or $-CO_2Me$; $-CON(R^{11}R^{12})$ especially $-CONH_2$; NO_2; $N(R^{11}R^{12})$ especially NMe_2; $-SOR^{13}$ especially -SOMe; $-SO_2N(R^{11}R^{12})$ especially $-SO_2NMe_2$ or halogen, especially F or Cl; and each of Ra, Rb, Rd and Re is H.

In the above-mentioned series of preferred compounds Ra to Re are all hydrogen, or one or two of Ra to Re are other than hydrogen whilst the others are hydrogen. For instance one of Ra, Rb and Rc is other than hydrogen. Alternatively Ra and Rc, or Rb and Rc, are other than hydrogen. Preferred values for the one or two of Ra to Re which is or are other than hydrogen include C_1-C_6 alkoxy such as OMe or OBu^n, halogen such as Cl or F, hydroxy, $-N(R^{11}R^{12})$, $-CO_2R^{11}$, $-CH_2SCOR^{13}$, $-CH_2SR^{11}$, $-NHCOR^{11}$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-NHCOCH_2OR^{11}$, $-NHCOCH_2OCOR^{13}$, $-CH_2NHCOOR^{13}$ and CF_3.

Particularly preferred compounds are those wherein Ra,

Rb, Rd and Re are each H, and Rc is selected from H, OMe -NHAc, $-CO_2H$, $-CO_2Me$, $-CONH_2$, NO_2, $-NMe_2$, SO_2Me, -SOMe and $-SO_2NMe_2$. Also preferred are compounds wherein Ra to Re are preferably each independently selected from H, halogen, hydroxy, C_1-C_6 alkoxy, nitro, $-CH_2SCOR^{13}$, $-CH_2SR^{11}$, $-CO_2R^{11}$, $-OCOR^{13}$, CF_3, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOR^{11}$, $-N(R^{11}R^{12})$, $-NHCO(CH_2)_nOCOR^{11}$, $-NHCO(CH_2)_nCO_2R^{11}$ and $-CH_2NHCO_2R^{13}$ or Ra and Rb, Rb and Rc, Rc and Rd, or Rd and Re, form a methylenedioxy group or form, with the carbon atoms to which they are attached, an optionally substituted benzene ring. Still more preferably, Ra and Rb are independently H, nitro or halogen, Rc is H, hydroxy, $-O(CH_2)_nN(R^{11}R^{12})$, $-OCOR^{13}$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, C_1-C_6 alkoxy, $-NHCO(CH_2)_nOR^{11}$, $-NHCO(CH_2)_nOCOR^{11}$, $-N(R^{11}R^{12})$, $-CH_2NHCO_2R^{13}$, $-CH_2SR^{11}$ or $-NHCOR^{11}$; Rd is H, halogen, C_1-C_6 alkoxy, $-CH_2SCOR^{13}$, $-CH_2SR^{11}$ or $-CO_2R^{11}$; and Re is H, nitro or halogen.

When any two adjacent groups of Ra to Re form, together with the carbon atom to which they are attached, a benzene ring, that ring is either unsubstituted or it may be substituted by any of the options specified above for Ra to Re. The benzene ring forms, together with the phenyl group, an optionally substituted naphthalene ring structure.

In one embodiment of formula (I) R^1 is a phenyl group as defined above which is unsubstituted or mono-substituted at position 2, 3 or 4 by Cl or MeO, or is a pyridyl, furyl or

thienyl group, R^2 is H, CH_3, cyclopropyl or phenyl, and one of R^3 and R^4 is H and the other is a group of formula (A) wherein q is 2 and each of R^5 and R^6 is a methoxy group.

In a second embodiment, R^1 is unsubstituted phenyl, R^2 is C_1-C_4 alkyl, preferably methyl, or is phenyl or cyclopropyl, R^3 is H and R^4 is a group of formula (A) wherein q is 2 and each of R^5 and R^6 is MeO.

In a third embodiment R^1 is substituted phenyl as defined above or a furyl, thienyl or pyridyl group, R^2 is H, R^3 is H and R^4 is a group of formula (A) wherein q is 2 and each of R^5 and R^6 is MeO.

In a fourth embodiment R^1 is substituted phenyl as defined above or a furyl, thienyl or pyridyl group, R^2 is H, R^3 is a group of formula (A) wherein q is 2 and each of R^5 and R^6 is MeO, and R^4 is H.

In a fifth embodiment R^1 is unsubstituted phenyl, R^2 is C_1-C_4 alkyl, preferably methyl, phenyl or cyclopropyl, R^3 is a group of formula (A) wherein q is 2 and each of R^5 and R^6 is MeO, and R^4 is H.

When in the above embodiments R^1 is a furyl, thienyl or pyridyl group it is preferably a 3-furyl, 2-thienyl, 3-thienyl or 4-pyridyl group.

Examples of preferred compounds of the invention are as follows. The compound numbering is adhered to in the rest of the specification.

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-

isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-ethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9112)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-benzyl-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9113)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-cyclopropylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9114)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(3-furylmethylene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9108)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(4-methoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9109)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(4-chlorobenzylidene)-1-methyl-2,5-dioxo-3-

piperazinylidene)methylbenzamide, hydrochloride (9091)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(2-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9092)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(3-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9093)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-pyridylmethylene)-3-piperazinylidene)methylbenzamide, hydrochloride (9110)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-thenylidene)-3-piperazinylidene)methylbenzamide, hydrochloride (9111)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-2,5-dioxo-6-(2-thenylidene)-3-piperazinylidene)methylbenzamide (9155)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-

isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-thenylidene)-3-piperazinylidene)methylbenzamide (9160)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9157)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z, 6Z)-6-(2-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9158)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-furylmethylene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9159)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-methoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9156)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-ethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9139)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-

isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-cyclopropylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9141)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-allyl-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9178)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-allyl-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9179)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9193)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(1-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9194)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(1-naphthyl)methylene-2,5-dioxo-3-

piperazinylidene)methylbenzamide (9195)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(2-furyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9196)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(2-furyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9197)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(1-methyl-3-pyrrolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9198)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(1-methyl-3-pyrrolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9199)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9209)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(1-methyl-3-indolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9210)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(3-methylbenzo(b)thien-2-yl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9211)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(1-methyl-3-indolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9214)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(3-methylbenzo(b)thien-2-yl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9215)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methoxycarbonylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9217)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-

4-((3Z,6Z)-1-methyl-6-(2-methylpropylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide (9228)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-cyclohexylmethylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9229)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-cyclohexylmethylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9230)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-pentylidene-3-piperazinylidene)methylbenzamide (9231)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)--3-((3Z,6Z)-1-methyl-2,5-dioxo-6-pentylidene-3-piperazinylidene)methylbenzamide (9232)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(2-methylpropylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide (9233)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(3,3-dimethylbutylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9234)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3,3-dimethylbutylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9235)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-((4S)-4-isopropenyl-1-cyclohexenyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9236)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-carboxymethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9241)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-((4S)-4-isopropenyl-1-cyclohexenyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9250)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-3-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-

piperazinylidene)methylbenzamide (9260)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9261)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-3-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-phenylpropylidene)-3-piperazinylidene)methylbenzamide (9266)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-phenylpropylidene)-3-piperazinylidene)methylbenzamide (9267)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(4-acetoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9272)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-acetoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9273)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(2-acetoxybenzylidene)-1-methyl-2,5-dioxo-3-

piperazinylidene)methylbenzamide (9274)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-(2-dimethylaminoethyl)-2,5-dioxo-3-piperazinylidene)methylbenzamide (9275)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(4-hydroxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9276)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-ethoxycarbonylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9299)

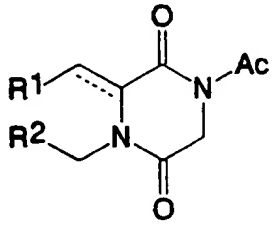
N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(2-hydroxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9300)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-hydroxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9301)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6E)-1-methyl-6-pentylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9306)

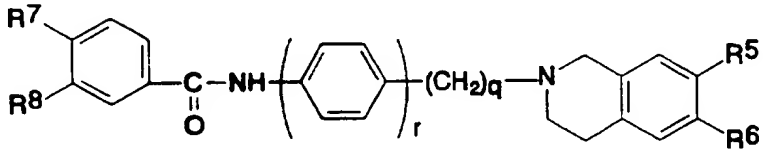
N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z)-1-methyl-6-benzyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9308)

Compounds of formula (I) may be prepared by a process which comprises treating a compound of formula (II):



(II)

wherein R^1, R^2 and ----- are as defined above, with a compound of formula (III):



(III)

wherein one of R^7 and R^8 is hydrogen and the other is -CHO, and q, r, R^5 and R^6 are as defined above; in the presence of a base in an organic solvent; and, if desired, converting the resulting compound into a pharmaceutically acceptable salt

thereof.

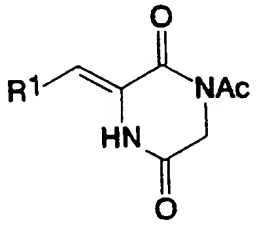
Suitable bases include caesium carbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium t-butoxide and triethylamine.

Suitable organic solvents include dimethylformamide (DMF), tetrahydrofuran (THF) and, in the case of potassium t-butoxide, t-butanol and mixtures thereof.

When DMF is used as solvent the temperature is typically between 0°C and reflux temperature, for example from 80°C-95°C when caesium carbonate is used as base.

When sodium hydride or potassium t-butoxide is used as the base the reaction mixture is typically warmed from 0°C to room temperature, or to 40°C. The reaction may be performed for a period of 1 to 4 hours, for example 2 or 3 hours.

The compounds of formula (II) wherein ----- is a double bond are prepared by a process which comprises treating a compound of formula (IV):

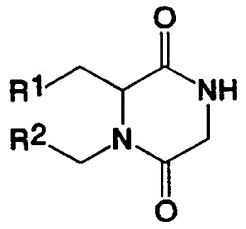


(IV)

wherein R^1 is as defined above, with an alkylating agent, in an organic solvent in the presence of a base. The alkylating agent is typically an alkyl halide R^2-CH_2X, a methanesulphonate or p-toluenesulphonate ester $R^2CH_2OSO_2Me$ or $R^2CH_2OSO_2C_6H_4Me$, respectively, or a dialkyl sulphate

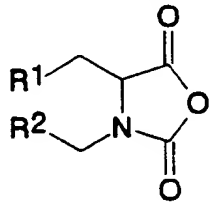
$(R^2CH_2O)_2SO_2$, wherein R^2 is as defined above and X is a halogen, for instance Cl Br or I. Suitable bases and solvents include sodium hydride in THF or DMF or mixtures thereof, and potassium t-butoxide in t-butanol or THF or DMF or mixtures thereof. The reaction mixture is typically warmed from 0°C to room temperature.

Compounds of formula (II) wherein ----- is a single bond may be prepared by treating a compound of formula (X):



(X)

wherein R^1 is as defined under (i) above and R^2 is as defined above with acetic anhydride. The reaction is typically performed under reflux, for instance for 1 to 6 hours, typically 3 hours. The compound of formula (X) may be prepared by treating a compound of formula (XI):

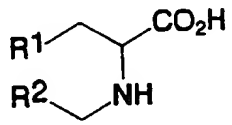


(XI)

with glycine methyl ester hydrochloride and triethylamine in a solvent, typically $CHCl_3$, at a low temperature, typically -50°C to -70°C, preferably -65°C, for 1 to 6 hours. This is followed by warming to room temperature overnight. The reaction mixture is then refluxed in a solvent such as toluene for 12-18 hours, typically 16 hours, to give the

desired compound of formula (X).

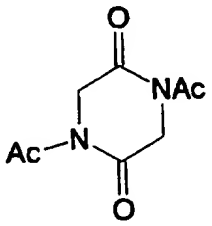
The compounds of formula (XI) may be prepared by treating a compound of formula (XII):



(XII)

with phosgene in THF at 0°C, followed by warming to room temperature overnight.

Compounds of formula (IV) may be prepared by a process which comprises treating 1,4-diacetyl-2,5-piperazinedione of formula (V):



(V)

with an aldehyde of formula:

R^1-CHO

wherein R^1 is as defined above, in the presence of a base in an organic solvent.

Suitable bases and solvents include triethylamine, caesium carbonate, sodium carbonate, potassium carbonate and sodium hydride in DMF or THF or mixtures thereof, and potassium t-butoxide in t-butanol or DMF or THF or mixtures

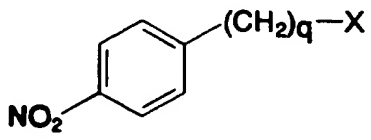
thereof.

When triethylamine in DMF is used the temperature of the reaction is typically from 100-140°C, for instance 120-130°C. When potassium t-butoxide is used as base the reaction mixture is typically warmed from 0°C to room temperature.

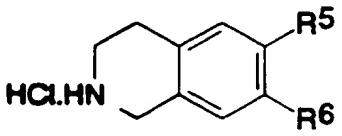
1,4-Diacetyl-2,5-piperazinedione may be prepared by the published procedure (S.M. Marcuccio and J.A. Elix, Aust. J. Chem., 1984, 37, 1791).

Compounds of formula (III) may be prepared by a process which comprises

(i) reacting together compounds of the following formulae (VI) and (VII):



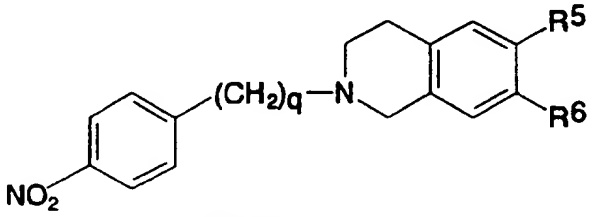
(VI)



(VII)

wherein q, R^5 and R^6 are as defined above and X is a halogen, in the presence of a base in an organic solvent;

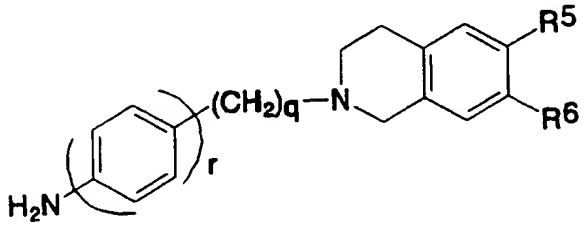
(ii) reducing the resulting compound of formula (VIII):



(VIII)

wherein q, R^5 and R^6 are as defined above; and

(iii) treating the resulting compound of formula (IX):



(IX)

wherein q, R^5 and R^6 are as defined above, and r is 1, with

(a) either 3-formylbenzoic acid in the presence of a coupling agent, or a derivative of 3-formylbenzoic acid in which the -COOH group has been activated by conversion to the acid halide group -COX in which X is a halogen, for instance F, Cl, Br or I, preferably Cl, or the mixed anhydride group -CO(OCOR') in which R' is C_1-C_6 alkyl; in both cases to give a compound of formula (III) wherein R^7 is hydrogen and R^8 is -CHO; or

(b) 4-formylbenzoic acid in the presence of a coupling agent, or a derivative of 4-formylbenzoic acid in which the -COOH group has been activated by conversion to the acid halide group -COX in which X is a halogen, for instance F, Cl, Br or I, preferably Cl, or the mixed anhydride group -CO(OCOR') in which R' is C_1-C_6 alkyl; in both cases to give a compound of formula (III) wherein R^7 is -CHO and R^8 is hydrogen.

When the 3- or 4-formylbenzoic acid has been activated by conversion of -COOH to -COX, the reaction is conducted in an organic solvent either with an excess of the amine of formula (IX), or in the presence of a base such as a

tertiary amine, e.g. Et_3N, or pyridine. The organic solvent is an inert organic solvent such as CH_2Cl_2.

When the 3- or 4-formylbenzoic acid has been activated by conversion of -COOH to -CO(OCOR'), the reaction with the compound of formula (IX) is conducted in an inert organic solvent such as CH_2Cl_2 or THF.

The coupling agent used in (a) or (b) with the 3- or 4-formylbenzoic acid, respectively, may be, for instance, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulphonate or 2-chloro-1-methylpyridinium iodide.

The activated acid halide or mixed anhydride derivative of 3- or 4-formylbenzoic acid may be produced by conventional methods. For instance, the acid halide derivative may be prepared by treatment of the carboxylic acid with a halogenating agent, for instance a chlorinating agent such as $SOCl_2$, PCl_3, oxalyl chloride or PCl_5. The mixed anhydride derivative may be prepared by treatment of the carboxylic acid with a C_1-C_6 alkyl haloformate such as iBuOCOCl or EtOCOCl, in the presence of a base such as Et_3N.

The reduction step (ii) is typically performed using iron powder and concentrated hydrochloric acid in methanol, usually at a temperature of about 80°C and for a period of 1 to 4 hours, for instance 3 hours. Alternatively it may be carried out by catalytic hydrogenation over a palladium on carbon catalyst in methanolic HCl, isopropanol or acetic acid.

Other starting compounds are known compounds or can be

readily synthesised from known compounds using conventional methods.

Compounds of formula (I) may be converted into pharmaceutically acceptable salts, and salts may be converted into the free compound, by conventional methods. Suitable salts include salts with pharmaceutically acceptable inorganic or organic acids. Examples of inorganic acids include hydrochloric acid, sulphuric acid and orthophosphoric acid. Examples of organic acids include p-toluenesulphonic acid, methanesulphonic acid, mucic acid and succinic acid.

Cancer cells which exhibit multi-drug resistance, referred to as MDR cells, display a reduction in intracellular drug accumulation compared with the corresponding drug-sensitive cells. Studies using in vitro derived MDR cell lines have shown that MDR is often associated with increased expression of a plasma membrane glycoprotein (P-gp) which has drug binding properties. P-gp is thought to function as an efflux pump for many hydrophobic compounds, and transfection studies using cloned P-gp have shown that its overexpression can confer the MDR phenotype on cells: see, for example, Ann. Rev. Biochem 58 137-171 (1989).

A major function of P-gp in normal tissues is to export intracellular toxins from the cell. There is evidence to suggest that overexpression of P-gp may play a clinical role in multi-drug resistance. Increased levels of P-gp mRNA or

protein have been detected in many forms of human cancers - leukaemias, lymphomas, sarcomas and carcinomas. Indeed, in some cases P-gp levels have been found to be increased in tumour biopsies obtained after relapse from chemotherapy.

Inhibition of P-gp function in P-gp mediated MDR has been shown to lead to a net accumulation of anti-cancer agent in the cells. For example, Verapamil a known calcium channel blocker was shown to sensitise MDR cells to Vinca alkaloids in vitro and in vivo: Cancer Res., 41, 1967-1972 (1981). The proposed mechanism of action involves competition with the anti-cancer agent for binding to the P-gp. A range of structurally unrelated resistance-modifying agents acting by this mechanism have been described such as tamoxifen (Nolvadex:ICI) and related compounds, and cyclosporin A and derivatives.

Compounds of formula I and their pharmaceutically acceptable salts (hereinafter referred to as "the present compounds") have been found in biological tests to have activity in modulating multi-drug resistance. The results are set out in Example 5 which follows. The present compounds may therefore be used as multi-drug resistance modifying agents, also termed resistance-modifying agents, or RMAs. The present compounds can modulate, e.g. reduce, or eliminate multi-drug resistance.

The present compounds can therefore be used in a method of potentiating the cytotoxicity of an agent which is cytotoxic to a tumour cell. Such a method comprises, for

instance, administering one of the present compounds to the tumour cell whilst the tumour cell is exposed to the cytotoxic agent in question. The therapeutic effect of a chemotherapeutic, or antineoplastic, agent may thus be enhanced. The multi-drug resistance of a tumour cell to a cytotoxic agent during chemotherapy may be reduced or eliminated.

The present compounds can also be used in a method of treating a disease in which the pathogen concerned exhibits multi-drug resistance, for instance multi-drug resistant forms of malaria (Plasmodium falciparum), tuberculosis, leishmaniasis and amoebic dysentery. Such a method comprises, for instance, administering one of the present compounds with (separately, simultaneously or sequentially) the drug to which the pathogen concerned exhibits multi-drug resistance. The therapeutic effect of the drug may thus be enhanced.

A human or animal patient harbouring a tumour may be treated for resistance to a chemotherapeutic agent by a method comprising the administration thereto of one of the present compounds. The present compound is administered in an amount effective to potentiate the cytotoxicity of the said chemotherapeutic agent. Examples of chemotherapeutic or antineoplastic agents which are preferred in the context of the present invention include Vinca alkaloids such as vincristine and vinblastine; anthracycline antibiotics such as daunorubicin and doxorubicin; mitoxantrone; actinomycin

D; taxanes e.g. taxol; epipodophyllotoxins e.g. etoposide and plicamycin.

In addition, a human or animal patient suffering from a disease in which the responsible pathogen exhibits multi-drug resistance may be treated for resistance to a therapeutic agent by a method comprising the administration thereto of one of the present compounds.

Examples of such disease include multi-drug resistant forms of malaria (Plasmodium falciparum), tuberculosis, leishmaniasis and amoebic dysentery.

MDR modulators also have utility in the delivery of drugs across the blood-brain barrier, and in the treatment of AIDS and AIDS-related complex. The present compounds can therefore be used in a method of facilitating the delivery of drugs across the blood brain barrier, and in the treatment of AIDS or AIDS related complex. A human or animal patient in need of such treatment may be treated by a method comprising the administration thereto of one of the present compounds.

The present compounds can be administered in a variety of dosage forms, for example orally such as in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The present compounds may therefore be given by injection or infusion.

The dosage depends on a variety of factors including

the age, weight and condition of the patient and the route of administration. Typically, however, the dosage adopted for each route of administration when a compound of the invention is administered alone to adult humans is 0.001 to 50 mg/kg, most commonly in the range of 0.01 to 5 mg/kg, body weight. Such a dosage may be given, for example, from 1 to 5 times daily by bolus infusion, infusion over several hours and/or repeated administration.

A piperazinedione derivative of formula (I) or a pharmaceutically acceptable salt thereof is formulated for use as a pharmaceutical or veterinary composition also comprising a pharmaceutically or veterinarily acceptable carrier or diluent. The compositions are typically prepared following conventional methods and are administered in a pharmaceutically or veterinarily suitable form. An agent for use as a modulator of multi-drug resistance comprising any one of the present compounds is therefore provided.

For example, the solid oral forms may contain, together with the active compound, diluents such as lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose, or polyvinyl pyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs, sweeteners; wetting agents such as

lecithin, polysorbates, lauryl sulphates. Such preparations may be manufactured in known manners, for example by means of mixing, granulating, tabletting, sugar coating, or film-coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. In particular, a syrup for diabetic patients can contain as carriers only products, for example sorbitol, which do not metabolise to glucose or which only metabolise a very small amount to glucose. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose or polyvinyl alcohol.

Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier such as sterile water, olive oil, ethyl oleate, glycols such as propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. Some of the present compounds are insoluble in water. Such compounds may be encapsulated within liposomes.

The invention will be further illustrated in the Examples which follow.

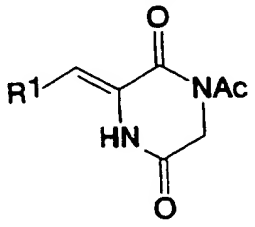
Reference Example 1: Preparation of starting compounds of formula (IV).

Method A

1,4-Diacetyl-2,5-piperazinedione (25.0g, 126 mmol) (S.M. Marcuccio and J.A. Elix, loc. cit.) was heated at 120-130°C in DMF (200 ml) with triethylamine (17.6 ml, 126 mmol) and benzaldehyde (13.0 ml, 126 mmol). After 4 h the mixture was cooled to room temperature and poured into EtOAc (1000 ml), and washed three times with brine. Any solid formed at this stage was filtered off. The filtrate was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was recrystallised from EtOAc:Hexane to give 11.78 g (38%) of 1-acetyl-3-benzylidene-2,5-piperazinedione. This compound of formula (IV) is listed as 1.1 in Table 1 below.

Following the same procedure, but replacing benzaldehyde by the appropriately substituted benzaldehyde R^1-CHO, where R^1 is as listed in Table 1A, the further starting compounds 1.2 to 1.10 were prepared:

TABLE 1A: Compounds of formula IV



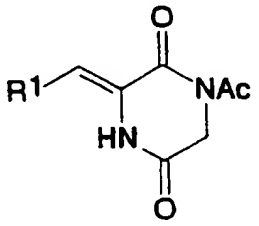
(IV)

Compound Number	R^1
1.1	phenyl
1.2	4-chlorophenyl
1.3	2-chlorophenyl
1.4	3-chlorophenyl
1.5	3-furyl
1.6	4-methoxyphenyl
1.7	3-pyridyl
1.8	3-thienyl
1.9	3-methoxyphenyl
1.10	2-thienyl

Method B

1,4-diacetyl-2,5-piperazinedione was treated with a series of benzaldehydes R^1-CHO, where R^1 is as listed in table 1B, in the presence of potassium t-butoxide in t-butanol-THF (1:1) at 0°C. The reaction mixture was allowed to warm to room temperature for the time indicated in the table. Recrystallisation, which was optional, was conducted using the indicated solvent.

TABLE 1B: Compounds of formula (IV)



(IV)

Compound Number	R^1	Reaction time (hours)	Recryst. solvent (if used)	Yield (%)
1.11	2-naphthyl	18		98
1.12	1-naphthyl	18		67
1.13	1-naphthyl	18		67
1.14	2-furyl	12		74
1.15	2-furyl	12		74
1.16	1-methyl-2-pyrrolyl	52	EtOAc	80
1.17	1-methyl-2-pyrrolyl	52	EtOAc	80
1.18	2-naphthyl	18		98
1.19	1-methyl-3-indolyl	14		33
1.20	3-methylbenzo[b]thien-2-yl	18		72
1.21	1-methyl-3-indolyl	14		33
1.22	3-methylbenzo[b]thien-2-yl	18		72
1.23	Me_2CH	12	EtOAc	48
1.24	Cyclohexyl	2		80
1.25	Cyclohexyl	2		80
1.26	n-Butyl	14	EtOAc	60
1.27	n-Butyl	14	EtOAc	60
1.28	Me_2CH	12	EtOAc	48
1.29	Me_3CCH_2	18	EtOAc	62
1.30	Me_3CCH_2	18	EtOAc	62
1.31	(4S)-4-isopropenyl-1-cyclohexenyl	18		
1.32	(4S)-4-isopropenyl-1-cyclohexenyl	18		
1.33	$4\text{-}AcOC_6H_4$	3		86
1.34	$3\text{-}AcOC_6H_4$	3	EtOAc-hexane	42
1.35	$2\text{-}AcOC_6H_4$	3	EtOAc-hexane	31
1.36	n-Butyl	14	EtOAc	60
1.37	$Ph\text{-}(CH_2)_2$	16		60

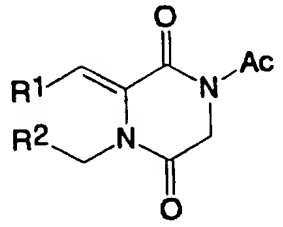
Reference Example 2: Preparation of starting compounds of formula (II) wherein ----- is a double bond

Method A

1-Acetyl-3-benzylidene-2,5-piperazinedione, compound 1.1 prepared in Reference Example 1, was treated with ethyl bromide and KOtBu/t-BuOH in DMF at a temperature of about 0°C and allowed to warm to room temperature to give 1-acetyl-3-benzylidene-4-ethyl-2,5-piperazinedione. This compound of formula (II) is listed as 2.1 in Table 2A below.

Further compounds of formula II were prepared by alkylating compounds 1.2 to 1.10, prepared in Reference Example 1, under the conditions set out in Table 2A:

Table 2A: Compounds of formula II



(II)

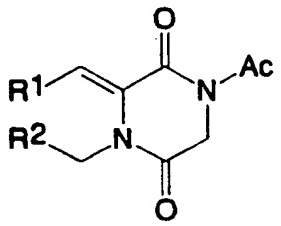
Compound Number	R^2	Starting Compound (IV)	Alkylation conditions
2.1	Me	1.1	(a) KOtBu/tBuOH, DMF, EtBr; 0°C to rt; or (b) 1.1 eq NaH, DMF: THF (1:5); 2 eq EtI, 0°C to rt; then column chromatography
2.2	Ph	1.1	KOtBu/tBuOH, DMF, $PhCH_2Cl$;
2.3	cyclo-propyl	1.1	(a) KOtBu/tBuOH, DMF, $C_3H_5CH_2Br$, 0°C to rt; or (b) 1.1 eq NaH, DMF:THF (1:5); 1.3 eq $C_3H_5CH_2Br$, 0°C to rt; reflux 6h; column chromatography
2.4	H	1.2	NaH, MeI, THF, DMF 0°C to rt
2.5	H	1.3	" "
2.6	H	1.4	" "
2.7	H	1.5	" "
2.8	H	1.6	" "
2.9	H	1.7	" "
2.10	H	1.8	" "
2.11	H	1.9	" "
2.12	H	1.10	" "

Method B

Compound 1.11 described in Reference Example 1 was treated, in THF-DMF (5:1), with sodium hydride and MeI at

0°C. The reaction mixture was allowed to warm to room temperature for 18 hours. The product was purified by recrystallisation from EtOAc to give the corresponding compound of formula (II) in 40% yield. Following this procedure, but replacing compound 1:11 by other compounds of formula IV described in Reference Example 1, and modifying the reaction time if necessary, the compounds listed in table 2B were prepared. Where indicated, purification was performed by flash chromatography or by recrystallisation as shown in the footnote.

TABLE 2B: Compounds of formula II



(II)

Compound Number	R^1	Starting Compound (IV)	Reaction time	Purification method (see footnote)	Yield (%)
2.13	H	1.11	18	a	40
2.14	H	1.12	18	b	8
2.15	H	1.13	18	b	8
2.16	H	1.14	18	a	50
2.17	H	1.15	18	a	50
2.18	H	1.16		b	26
2.19	H	1.17		b	26
2.20	H	1.18	18	a	40
2.21	H	1.19	72	b	18
2.22	H	1.20	16	c	10

2.23	H	1.21	72	b	18
2.24	H	1.22	16	c	10
2.25	H	1.23	18	d	73
2.26	H	1.24	14	d	86
2.27	H	1.25	14	d	86
2.28	H	1.26		d	75
2.29	H	1.27		d	75
2.30	H	1.28	18	d	73
2.31	H	1.29	18	d	70
2.32	H	1.30	18	d	70
2.33	H	1.31		d	46
2.34	H	1.32		d	46
2.35	H	1.33	3	b	33
2.36	H	1.34	72	b	20
2.37	H	1.35	3	b	45
2.38	H	1.36		d	75
2.44	H	1.37	16	e	37

Footnote

a = recrystallisation from EtOAc

b = flash chromatography with EtOAc-hexane (1:1)

c = flash chromatography with CH_2Cl_2

d = flash chromatography with Et_2O-hexane (1:1)

e = recrystallisation from EtOAc-hexane

Method C

Compound 1.1, described in Reference Example 1, was treated with Cs_2CO_3 (2eq.), Me_3SiCl (1 eq.) and allyl bromide (1 eq.) in acetonitrile at 0°C. The reaction mixture was allowed to warm to room temperature for 5 hours. Flash

chromatography of the product using 20% EtOAc in hexane gave 2.39 in 50% yield, which is a compound of formula (II) in which R^2 is $-CH=CH_2$.

Method D

Compound 1.1, described in Reference Example 1, was treated in THF-DMF (5:1) with sodium hydride and methyl bromoacetate at 0°C. The reaction mixture was allowed to warm to room temperature for 3 hours. The product was purified by recrystallisation from EtOAc-hexane to give 2.40 in 35% yield, which is a compound of formula (II) in which R^2 is $-CO_2Me$.

Method E

Compound 1.1, described in Reference Example 1, was treated in DMF with sodium hydride and 2-dimethylaminoethyl chloride hydrochloride at 0°C. The reaction mixture was warmed to 20°C, and then further warmed to 80°C, over a period of 5 hours. The product was purified by recrystallisation from 1% MeOH in EtOAc to give 2.41 in 32% yield, which is a compound of formula (II) wherein R^2 is $-CH_2NMe_2$.

Method F

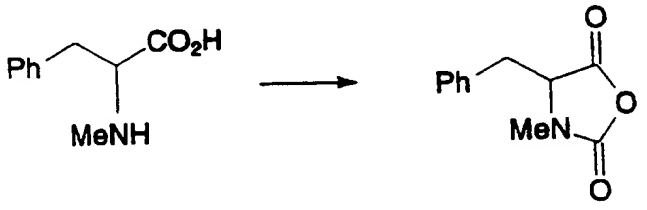
Compound 1.1, described in Reference Example 1, was treated in acetonitrile with Cs_2CO_3 and ethyl bromoacetate at -20°C. The reaction mixture was warmed to 20°C for 2 hours.

The product was purified by flash chromatography using EtOAc-hexane (1:2) to give 2.42 in 35% yield, which is a compound of formula (II) wherein R^2 is $-CO_2Et$.

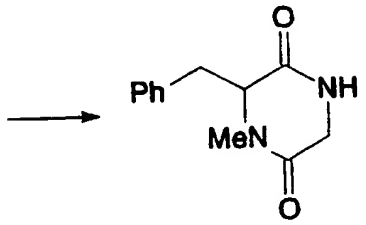
Reference Example 3: Preparation of a compound of formula (II) wherein ----- is a single bond

1-methyl-6-benzyl-2,5-piperazinedione was treated with acetic anhydride under reflux for 3 hours to give compound 2.43 in 98% yield, which is a compound of formula (II) wherein ----- is a single bond, R^1 is Ph and R^2 is H.

Reference Example 4: Preparation of 1-methyl-6-benzyl -2,5-piperazinedione



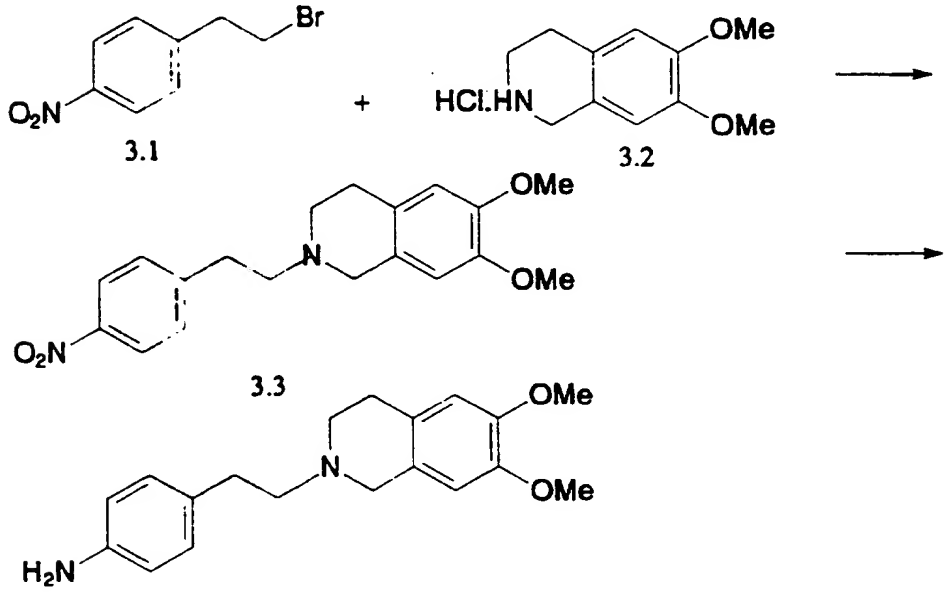
(i) (ii)



Compound (i) was treated with phosgene in THF at 0°C for 15 minutes. The reaction mixture was then warmed to room temperature overnight. The resulting compound (ii) was treated with glycine methyl ester hydrochloride and triethylamine in $CHCl_3$ at -65°C for 3 hours. The reaction mixture was allowed to warm to room temperature overnight and was then refluxed for 16 hours in toluene to give the desired product in 53% yield.

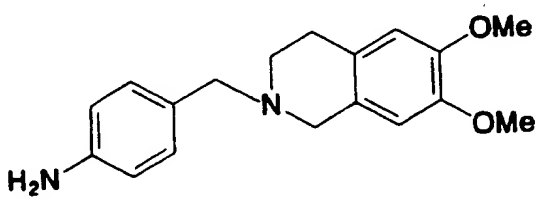
Reference Example 5: Preparation of 4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)aniline

(a) The title compound, which is a compound of formula (IX), was prepared according to the following scheme:

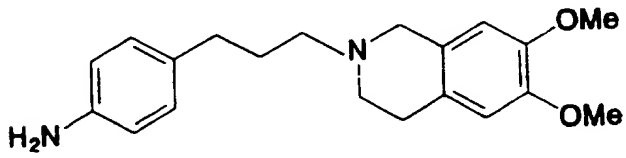


Compound 3.1 was treated with 3.2 in the presence of K_2CO_3 in DMF, at a temperature of 100°C for 12 hours, to give 3.3 in 78% yield. 3.3 was then reduced with Fe powder in concentrated HCl and MeOH at 80°C for 3 hours to give 3.4 in 51% yield. Alternatively 3.3 was reduced by catalytic hydrogenation at 30psi over a palladium on carbon catalyst in methanolic HCl for 3 hours to give 3.4 in quantitative yield.

(b) Following the synthetic route described under (a), but replacing compound 3.1 by 4-bromomethylbenzoic acid and 4-(3-bromopropyl)benzoic acid, respectively, the following two further compounds of formula (IX) were prepared:

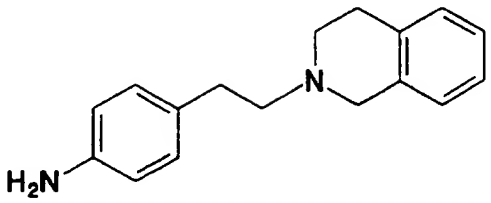


(3.5)



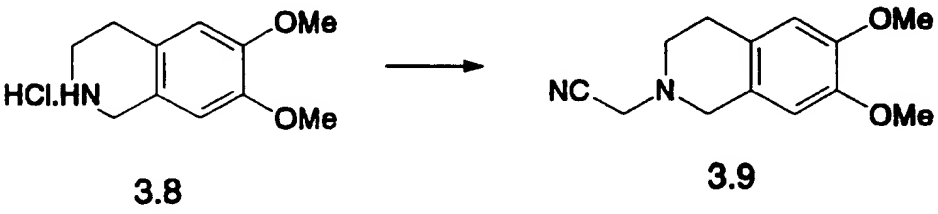
(3.6)

(c) Following the synthetic route described under (a), but replacing compound 3.2 by 1,2,3,4-tetrahydroisoquinoline hydrochloride, the following further compound of formula (IX) was prepared:

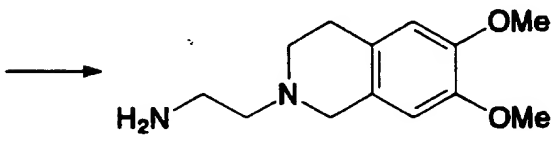


(3.7)

(d) An amine of formula (IX) in which r is 0, compound 3.10, was prepared as follows:



3.8 3.9

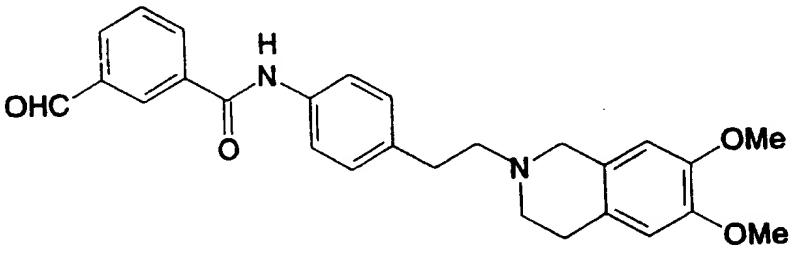


3.10

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (3.8) was treated with chloroacetonitrile in the presence of K_2CO_3 in acetonitrile under reflux for 24 hours. Compound 3.9 was obtained in 92% yield. 3.9 was then treated with $LiAlH_4$ in ethylene glycol dimethyl ether at room temperature overnight. The temperature was then raised to 40°C and the reaction continued for 30 minutes. The desired amine 3.10 was obtained in 98% yield.

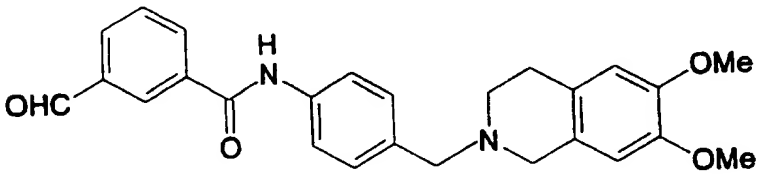
Example 1: Preparation of compounds of formula III Method 1

Compound 3.4 prepared according to Reference Example 5 was treated with 2-chloro-1-methylpyridinium iodide and 3-formylbenzoic acid in CH_2Cl_2 in the presence of Et_3N at a temperature of about 0°C and allowed to warm to room temperature overnight to afford the following compound of formula III in 43% yield:

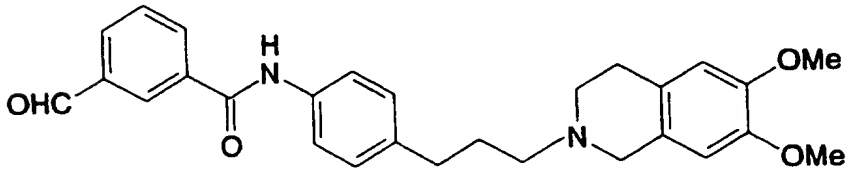


4.1

Following the same procedure, but replacing compound 3.4 by compounds 3.5 and 3.6, respectively, the following two further compounds of formula III were prepared:



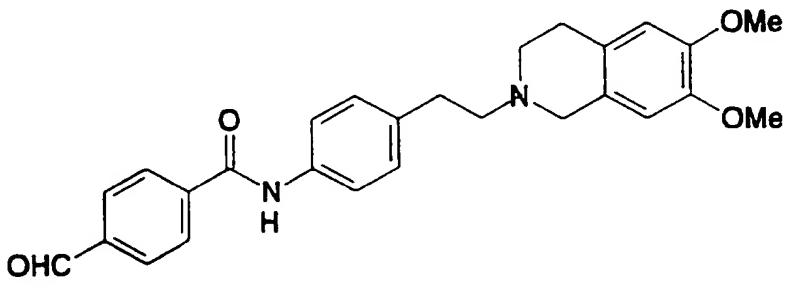
4.3



4.4

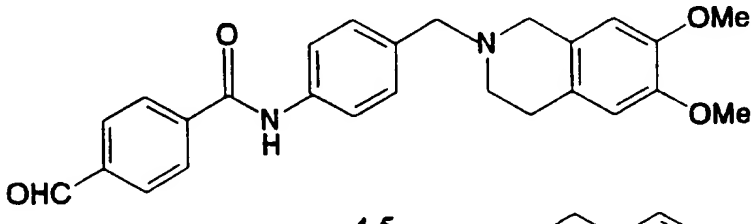
Method 2

4-formylbenzoyl chloride was prepared by treating 4-formylbenzoic acid with thionyl chloride in toluene under reflux. It was then treated with compound 3.4, prepared according to Reference Example 5, in CH_2Cl_2 in the presence of Et_3N at a temperature of about 0°C and allowed to warm to room temperature, to afford the following compound 4.2 in 53% yield:

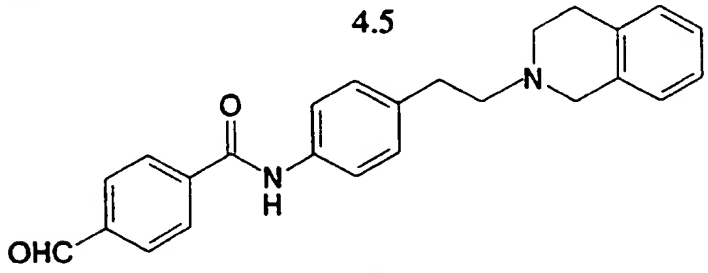


4.2

Following the same procedure, but replacing compound 3.4 by compounds 3.5 and 3.7, respectively, the following two further compounds of formula III were prepared:



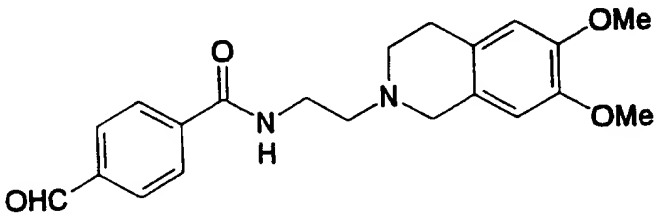
4.5



4.6

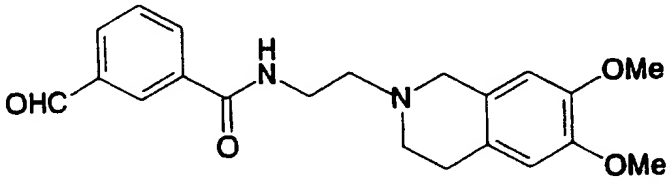
Method 3

4-formylbenzoyl chloride, as described in Method 2 above, was treated with Et_3N in CH_2Cl_2 at a temperature of -20°C. Compound 3.10 prepared according to Reference Example 5 was then added. Following aqueous work-up and purification by flash chromatography, the following compound 4.7 was obtained in 43% yield:



4.7

Following the same procedure, but replacing 4-formylbenzoyl chloride by 3-formylbenzoyl chloride, the following compound 4.8 was obtained in 48% yield:



4.8

Example 2: Preparation of compounds of formula (I)

By reacting together a compound of formula (II), prepared in Reference Example 2, and a compound of formula (III), prepared in Example 1, the following compounds of the invention were prepared under the conditions set out in Table 3A:

Table 3A: Compounds of formula (I)

Compound (I) N°	Compound II	Compound III	Conditions
9112	2.1	4.2	KOtBu, tBuOH, THF, 0°C to rt
9113	2.2	4.2	"
9114	2.3	4.2	"
9091	2.4	4.2	Cs_2CO_3, DMF, 90°C, 2-3 hours
9092	2.5	4.2	"
9093	2.6	4.2	"
9108	2.7	4.2	"
9109	2.8	4.2	"
9110	2.9	4.2	"
9111	2.10	4.2	"
9155	2.12	4.1	Cs_2CO_3, DMF, 90°C, 2-3 hours
9156	2.11	4.1	"
9157	2.6	4.1	"
9158	2.5	4.1	"
9159	2.7	4.1	"

9160	2.10	4.1	"
9139	2.1	4.1	Cs_2CO_3, DMF, 80°C, 2-3 hours
9141	2.3	4.1	"

Example 3: Preparation of salts

The compounds prepared in Example 2 were converted to the corresponding hydrochloride salts by treatment with gaseous HCl in THF.

Example 4: Preparation of compounds of formula (I)

By reacting together a compound of formula (II), prepared in Reference Example 2 or 3, and a compound of formula (III), prepared in Example 1, in DMF at 80°C in the presence of Cs_2CO_3 for the time specified in Table 4, the compounds of formula (I) listed in the Table were prepared. Some of the compounds were purified by recrystallisation or flash chromatography, also as indicated in Table 4.

TABLE 4: Compounds of formula (I)

Compound (I)	Compound (II)	Compound (III)	Reaction time (h)	Purification solvent or eluent (see footnote)
9178	2.39	4.2	3	5% H_2O in PrOH (a)
9179	2.39	4.1	3	5% H_2O in PrOH (a)
9193	2.13	4.2	16	EtOAc (a)
9194	2.14	4.2	5	EtOAc (a)
9195	2.15	4.1	5	EtOAc (a)
9196	2.16	4.2	16	
9197	2.17	4.1	16	
9198	2.18	4.2	14	nPrOH (a)

9199	2.19	4.1	10	iPrOH (a)
9209	2.20	4.1	10	EtOAc (a)
9210	2.21	4.2	12	EtOAc-MeOH (a)
9211	2.22	4.1	14	MeOH, EtOAc, Et_2O (a)
9214	2.23	4.1	18	CH_2Cl_2-Et_2O (a)
9215	2.24	4.2	4	EtOAc-Et_2O (a)
9217	2.40	4.1	2	EtOAc-hexane (a)
9228	2.25	4.2	8	5% MeOH in Et_2O (b)
9229	2.26	4.2	14	5% MeOH in Et_2O (b)
9230	2.27	4.1	18	5% MeOH in Et_2O (b)
9231	2.28	4.2	14	
9232	2.29	4.1	14	5% MeOH in Et_2O (b)
9233	2.30	4.1	5	5% MeOH in Et_2O (b)
9234	2.31	4.2	18	5% MeOH in Et_2O (b)
9235	2.32	4.1	14	5% MeOH in Et_2O (b)
9236	2.33	4.2	14	5% MeOH in Et_2O (b)
9250	2.34	4.1	14	5% MeOH in Et_2O (b)
9260	2.13	4.7	4	
9261	2.13	4.8	4	EtOAc-heptane (a)
9266	2.44	4.8	16	EtOAc-hexane (a)
9267	2.44	4.7	16	
9272	2.35	4.1	3	EtOAc-hexane (a)
9273	2.36	4.1	2	EtOAc-hexane (a)
9274	2.37	4.1	3	EtOAc-hexane (a)
9275	2.41	4.1	3	EtOAc-hexane (a)
9299	2.42	4.1	3	

9306	2.38	4.1	14	5% MeOH in Et_2O (b)
9308	2.43	4.1	16	10% MeOH in EtOAc (b)

Footnote

(a) Recrystallisation solvent

(b) Flash chromatography eluent

Example 5: Preparation of Salts

Selected compounds prepared in Example 4 were converted to the corresponding hydrochloride salts by treatment with gaseous HCl in CH_2Cl_2. The hydrochloride, denoted in Table 5 below by the suffix ".HCl" was in some cases then recrystallised as shown in the table.

TABLE 5: Hydrochloride salts

Salt	Recrystallisation solvent	Yield (%)
9193.HCl		
9144.HCl	EtOAc	21
9195.HCl	EtOAc	22
9196.HCl		
9197.HCl	EtOAc	35
9232.HCl		
9306.HCl		

Example 6: Interconversions of compounds of formula (I)

Compounds of formula (I) were prepared by treating selected compounds of formula (I) prepared in Example 4 with appropriate reagents using conventional synthetic techniques, as follows:

1. 9217 was treated with LiOH in aqueous THF at room temperature for 2 hours to give compound 9241.

2. 9272 was treated with $NaBH_4$ in MeOH at 0°C for 2 hours to give compound 9276 in 73% yield.

3. 9274 was treated with $NaBH_3CN$ in MeOH and THF at 0°C. The reaction mixture was then warmed to 50°C over 5 hours, and the product recrystallised from 20% EtOH in EtOAc to give compound 9300 in 58% yield.

4. 9273 was treated with $NaBH_3CN$ in MeOH and THF at reflux for 7 hours. The product was recrystallised from EtOAc-hexane (1:5) to give compound 9301 in 18% yield.

Example 7: Pharmaceutical Composition

Tablets, each weighing 0.15 g and containing 25 mg of a compound of formula (I) or salt thereof can be manufactured as follows:

Composition for 10,000 tablets

compound of formula (I) or salt thereof (250 g)

lactose (800 g)

corn starch (415 g)

talc powder (30 g)

magnesium stearate (5 g)

The compound of formula (I) or salt thereof, lactose and half of the corn starch are mixed. The mixture is then forced through a sieve 0.5 mm mesh size. Corn starch (10 g) is suspended in warm water (90 ml). The resulting paste is used to granulate the powder. The granulate is dried and broken up into small fragments on a sieve of 1.4 mm mesh size. The remaining quantity of starch, talc and magnesium stearate is added, carefully mixed and processed into tablets.

Example 8: Testing of compounds of formula (I) and their salts as modulators of MDR

Materials and Methods

The EMT6 mouse mammary carcinoma cell line and the MDR resistant subline AR 1.0 were cultured in RPMI 1640 medium containing 10% foetal calf serum and 2mM glutamine at 37°C in 5% CO_2. Cells were passaged between 1 in 200 and 1 in 2000 in the case of the parental cell line and between 1 in 20 and 1 in 200 in the case of the MDR resistant subline, after trypsinisation (0.25% trypsin, 0.2gl^{-1}, EDTA).

1. Drug accumulation assay

AR 1.0 cells were seeded into 96 well opaque culture plates (Canberra Packard). The assay medium contained a mixture of tritiated Daunorubicin (DNR), a cytotoxic agent, and unlabelled DNR (0.3 μ Ci/ml; 2μM). Compounds of formula I were serially diluted in assay medium over a range of concentrations from 5 nM to 100 μM. The cells were incubated at 37°C for 1 hr before washing and determination of cell associated radioactivity. Results are expressed as % maximum accumulation where 100% accumulation is that observed in the presence of the known RMA verapamil at a concentration of 100 μM or as an IC_{50}.

The results are set out in the following Table 6.

TABLE 6

Compound No.	IC_{50} (μM) Accumulation	Maximum (%) Accumulation
9091	2.0	
9092	1.2	
9093	3.0	
9108	0.7	
9109	2.0	
9110	2.0	
9111	1.0	
9112	0.2	
9113	5.0	
9114	0.6	
9139	0.2	
9141	0.5	
9155	0.06	
9156	0.1	

9157	0.2	
9158	0.6	
9159	0.4	
9160		20%
9178	0.080	
9179	0.170	
9193.HCl	7.0	
9194.HCl	1.800	
9195.HCl	0.210	
9196.HCl	0.140	
9197.HCl	0.025	
9198	0.200	
9199	0.140	
9209	0.600	
9210	0.220	
9211	1.400	
9214	0.070	
9215	1.100	
9217	0.700	
9228	0.350	
9229	0.200	
9230	0.130	
9231	2.000	
9232	0.020	
9233	0.600	
9234	0.500	
9235	0.600	
9236	2.000	
9250	0.800	
9260	0.800	
9261	1.200	
9266	1.200	

9267	5.000	
9272	0.400	
9273	0.070	
9274	0.800	
9275	0.600	
9276	1.900	
9276.HCl	0.700	
9299	0.500	
9300	0.200	
9301	0.200	
9308	3.000	

2. Potentiation of Doxorubicin toxicity

Compounds of formula (I) were examined for their ability to potentiate the toxicity of doxorubicin in AR 1.0 cells. In initial proliferation assays compounds were titrated against a fixed concentration of doxorubicin (0.86μM) which alone is non-toxic to AR 1.0 cells. After a four day incubation with doxorubicin proliferation was measured using the colorimetric sulphorhodamine B assay (Skehan et al; J.Natl. Cancer Inst. 82 pp 1107-1112 (1990)). The results are shown in Table 7.

Compounds which were shown to be able to sensitise AR 1.0 cells to 0.86μM doxorubicin without high innate toxicity were selected for further study. Cells were cultured for four days with concentrations of doxorubicin over the range of 0.01 nM-50 μM in the presence of fixed concentrations of compounds of formula (I). Proliferation was quantified as

described by Skehan et al, loc cit. The IC_{50} (concentration required to reduce proliferation to 50% of the untreated controls) for doxorubicin alone and for the compounds of formula (I) were derived and used to calculate the potentiation index (PI):

$$PI = \frac{IC_{50} \text{ for Doxorubicin alone}}{IC_{50} \text{ for Doxorubicin plus RMA}}$$

The results are shown in Table 8:

TABLE 7

Compound No.	Compound toxicity (IC_{50} μM)	Toxicity with cytotoxic agent (IC_{50} μM)
9091	1.8	0.15
9092	0.7	0.07
9093	2.0	0.09
9108	4.0	0.10
9109	4.0	0.30
9110	6.0	1.00
9111	2.5	0.15
9112	2.0	0.015
9113	0.4	0.1
9114	1.0	0.06
9139	4	0.3
9141	2	0.3
9178	1.50	0.008
9179	0.50	0.080
9193.HCl	2.00	0.200
9194.HCl	6.00	0.050

9195.HCl	1.00	0.010
9196.HCl	7.00	0.060
9197.HCl	28.00	0.010
9198	8.00	0.020
9199	40.00	0.050
9209	45.00	0.070
9210	40.00	0.080
9211	50.00	0.080
9214	100.00	0.008
9215	10.00	0.030
9228	0.60	0.100
9229	0.50	0.070
9330	0.45	0.100
9231	2.00	0.120
9232	3.00	0.060
9233	8.00	0.400
9234	1.00	0.080
9235	0.50	0.100
9236	0.80	0.130
9250	2.00	0.080
9260	3.00	0.350
9261	5.00	0.400
9272	9.00	0.200
9273	20.00	0.020
9274	40.00	0.050
9275	1.80	0.700
9276	30.00	0.500

TABLE 8

Compound No.	Potentiation index	PI determined at (μM)
9108	1000	1
9109	250	1
9111	500	1
9112	1000	1
9139	500	0.5
9141	285	0.5
9155	67	0.2
9156	25	0.2
9157	40	0.2
9158	75	0.2
9159	50	0.2
9178	7.1 27.3 69.8 250.0	0.01 0.03 0.10 0.30
9193.HCl	20.0 2.0	0.30 0.10
9194.HCl	50.0 7.5 1.5 1.2	0.30 0.10 0.03 0.01
9195.HCl	454.0 50.0 2.5 1.2	0.30 0.10 0.03 0.01
9196.HCl	37.5 5.0 1.5 1.0	0.30 0.10 0.03 0.10
9197.HCl	65.0 4.3 1.3 1.3	0.30 0.10 0.03 0.10
9198	32.5 3.3 1.3 1.3	0.30 0.10 0.03 0.01

9199	65.0 2.2 1.3 1.3	0.30 0.10 0.03 0.01
9209	125.0 15.0 1.2 1.2	0.30 0.10 0.03 0.01
9210	75.0 8.3 1.5 1.3	0.30 0.10 0.03 0.01
9211	1538.0 1000.0	1.00 0.50
9214	200.0 150.0 20.0 2.0	0.30 0.10 0.03 0.01
9215	66.7 15.0 3.0 1.5	0.30 0.10 0.03 0.01
9217	11.0 1.0 0.9 0.8	0.30 0.10 0.03 0.01
9231	20.0 3.0 0.9 1.1	0.30 0.10 0.03 0.01
9232	80.0 20.0 3.0 1.0	0.30 0.10 0.03 0.01
9234	50.0 5.0	0.30 0.10
9235	37.5 2.3	0.30 0.10
9236	16.7 2.1	0.30 0.10
9250	286.0	0.50
9260	3.3 2.0	0.30 0.10

9261	2.2 1.7	0.30 0.10
9272	175.0 5.6 1.4	1.00 0.30 0.10
9273	100.0 96.1 83.3 29.4	3.00 1.00 0.30 0.10
9274	100.0 90.9 71.4 25.0	3.00 1.00 0.30 0.10
9275	25.0 6.9 0.7	1.00 0.30 0.10
9276	166.6 25.0 0.8 0.8	3.00 1.00 0.30 0.10
9299	16.0 1.8	0.30 0.10
9300	133.3 61.5 10.0	1.00 0.30 0.10
9301.HCl	133.3 88.9 28.6	1.00 0.30 0.10

Example 6: **Characterisation of the present compounds**

The compounds and salts prepared in Examples 1 and 2 were characterised by mass spectroscopic and proton nmr techniques. The results are set out in Tables 9 and 10:

TABLE 9

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9091	$C_{39}H_{37}ClN_4O_5.HCl$	679(10), 677(10), 208(100)	CI	d_6-DMSO/300MHz	2.5-4.7 (10H,m), 2.95 (3H,s), 3.83 (6H,s), 6.88 (1H,s), 6.92 (1H,s), 6.98 (1H,s), 7.15 (1H,s), 7.40 (2H,d), 7.51 (2H,d), 7.59 (2H,d), 7.83 (2H,d), 7.90 (2H,d), 8.12 (2H,d), 10.45 (1H,s), 10.8 (1H,s), 11.1 (1H,bs)
9092	$C_{39}H_{37}ClN_4O_5.HCl$	679(10), 677(10), 208(100)	CI	d_6-DMSO/300MHz	2.5-3.7 (8H,m), 2.88 (3H,s), 3.84 (6H,s), 4.5 (2H,m), 6.89 (1H,s), 6.93 (1H,s), 7.01 (1H,s), 7.15 (1H,s), 7.40 (2H,d), 7.50 (3H,m), 7.65 (1H,m), 7.82 (2H,d), 7.90 (2H,d), 8.14 (2H,d), 10.47 (1H,s), 10.90 (1H,s), 11.37 (1H,bs)
9093	$C_{39}H_{37}ClN_4O_5.HCl$	679(10), 677(5), 208(100), 190(100)	CI	d_6-DMSO/300MHz	2.3-4.7 (10H,m), 2.94 (3H,s), 3.84 (6H,s), 6.89 (1H,s), 6.93 (1H,s), 6.99 (1H,s), 7.16 (1H,s), 7.40 (2H,d), 7.42-7.60 (4H,m), 7.82 (2H,d), 7.90 (2H,d), 8.14 (2H,d), 10.45 (1H,s), 10.85 (1H,s), 11.30 (1H,bs)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9108	$C_{37}H_{36}N_4O_6$.HCl	633(25), 439(40), 206(85), 91(100)	CI	d_6-DMSO/300MHz	3.0-4.7 (10H,m), 3.2 (3H,s), 3.7 (2x3H,s), 6.74 (1H,s), 6.90 (1H,s), 6.94 (2x1H,s), 7.00 (1H,s), 7.41 (2H,d), 7.80 (2H,d), 7.85 (1H,s), 7.86 (2H,d), 8.08 (1H,s), 8.09 (2H,d), 10.43 (1H,s)
9109	$C_{40}H_{33}N_4O_6$	673(2), 672(5), 246(25), 206(100), 164(90), 91(60)	CI	d_6-DMSO/300MHz	2.9-4.0 (10H,m), 3.00 (3H,s), 3.81 (2x3H,s), 3.89 (3H,s), 6.81 (1H,s), 6.83 (1H,s), 6.95 (1H,s), 7.09 (2H,d), 7.13 (1H,s), 7.37 (2H,d), 7.41 (2H,d), 7.81 (2x2H,d), 8.09 (2H,d), 10.40 (1H,s)
9110	$C_{38}H_{37}N_5O_5$.2HCl			d_6-DMSO/300MHz	2.96 (3H,s), 3.0-4.7 (10H,m), 3.84 (2x3H,s), 6.90 (1H,s), 6.93 (1H,s), 7.01 (1H,s), 7.19 (1H,s), 7.42 (2H,d), 7.83 (5H,m), 8.12 (3H,m), 8.73 (1H,d), 8.85 (1H,s), 10.45 (1H,s)
9111	$C_{37}H_{36}N_4O_5S$.HCl	649(30), 456(30), 337(50), 208(100), 164(60)	CI	d_6-DMSO/300MHz	3.0-4.0 (8H,m), 3.07 (3H,s), 3.84 (2x3H,s), 4.41 (2H,bs), 6.88 (1H,s), 6.92 (1H,s), 6.96 (1H,s), 7.14 (1H,s), 7.29 (1H,d), 7.41 (2H,d), 7.71 (1H,dd), 7.77 (1H,m), 7.81 (2H,d), 7.85 (2H,d), 8.10 (2H,d), 10.45 (1H,s)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9112	$C_{40}H_{40}N_2O_5.HCl$	657(7), 286 (60), 269 (100)	CI	d_6-DMSO/300MHz	0.99 (3H,t), 3.0-4.7 (10H,m), 3.67 (2H,q), 3.84 (3H,s), 3.86 (3H,s), 6.90 (1H,s), 6.93 (1H,s), 7.01 (1H,s), 7.22 (1H,s), 7.42 (2H,d), 7.52 (5H,m), 7.82 (2H,d), 7.90 (2H,d), 8.14 (2H,d), 10.45 (1H,s), 11.20 (1H,bs)
9113	$C_{45}H_{42}N_4O_5.HCl$	719(25), 286(60), 269(100)	CI	d_6-DMSO/300MHz	3.0-4.7 (10H,m), 3.85 (2x3H,s), 4.85 (2H,s), 6.92 (4H,m), 7.04 (1H,s), 7.20 (1H,s), 7.33 (3H,m), 7.40 (2H,d), 7.55 (5H,m), 7.85 (2H,d), 7.91 (2H,d), 8.14 (2H,d), 10.45 (1H,s), 10.83 (1H,s), 11.25 (1H,bs)
9114	$C_{42}H_{42}N_4O_5.HCl$	683(20), 206(40), 167(80), 149(100), 57(40)	CI	d_6-DMSO/300MHz	0.0-1.1 (5H,m), 3.0-4.7 (12H,m), 3.87 (2x3H,s), 6.90 (1H,s), 6.94 (1H,s), 7.01 (1H,s), 7.20 (1H,s), 7.40 (2H,d), 7.52 (5H,m), 7.85 (2H,d), 7.90 (2H,d), 8.13 (2H,d), 10.45 (1H,s), 10.80 (1H,s), 10.90 (1H,bs)
9139	$C_{40}H_{40}N_4O_5$	657(34), 431(57), 206(83), 190(100)	CI	$CDCl_3$/400MHz	0.96 (3H,t), 2.72-2.94 (8H,m), 3.63 (2H,s), 3.67 (2H,q), 3.84 (2x3H,s), 6.55 (1H,s), 6.60 (1H,s), 7.09 (1H,s), 7.18 (1H,s), 7.20-7.52 (8H,m), 7.55 (4H,m), 7.83 (1H,d), 7.99 (1H,s), 8.13 (1H,s)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9141	$C_{42}H_{42}N_4O_5$	683(8), 614(62), 190(100)	CI	$CDCl_3$/400MHz	0.05 (2H,d), 0.35 (2H,d), 0.97 (1H,m), 2.70-2.90 (8H,m), 3.53 (2H,d), 3.63 (2H,s), 3.83 (2x3H,s), 6.55 (1H,s), 6.60 (1H,s), 7.05 (1H,s), 7.11 (1H,s), 7.20-7.65 (12H,m), 7.82 (1H,d), 8.00 (1H,s), 8.13 (1H,s)
9156	$C_{40}H_{40}N_4O_6$			$CDCl_3$/400MHz	2.74-2.95 (8H,m), 3.01 (3H,s), 3.68 (2H,s), 3.82-3.85 (9H,m), 6.54 (1H,s), 6.62 (1H,s), 6.80 (1H,s), 6.82-6.90 (2H,m), 7.10 (1H,s), 7.20-7.33 (5H,m), 7.54-7.60 (4H,m), 7.83 (1H,m), 7.97 (1H,s), 8.08 (1H,s)
9157	$C_{39}H_{37}ClN_4O_5$			$CDCl_3$/400MHz	2.73-2.94 (8H,m), 3.00 (3H,s), 3.66 (2H,s), 3.84 (2x3H,s), 6.55 (1H,s), 6.62 (1H,s), 7.12 (1H,s), 7.20 (1H,s), 7.23-7.28 (3H,m), 7.32 (d,2H), 7.53-7.60 (6H,m), 7.82 (1H,m), 7.92 (1H,s), 7.97 (1H,s)
9158	$C_{39}H_{37}ClN_4O_5$	677(100)	ESI	$CDCl_3$/400MHz	2.73-2.93 (11H,m), 3.64 (2H,s), 3.84 (2x3H,s), 6.56 (1H,s), 6.61 (1H,s), 7.12 (1H,s), 7.19-7.31 (7H,m), 7.45 (1H,m), 7.54-7.59 (4H,m), 7.84 (1H,m), 7.96 (1H,s), 8.00 (1H,s)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9159	$C_{37}H_{36}N_4O_6$	633(100)	ESI	$CDCl_3$/400MHz	2.73-2.93 (8H,m), 3.18 (3H,s), 3.65 (2H,s), 3.84 (2x3H,s), 6.43 (1H,s), 6.56 (1H,s), 6.61 (1H,s), 7.00 (1H,s), 7.06 (1H,s), 7.23 (2H,d), 7.48 (1H,m), 7.52-7.59 (4H,m), 7.83 (1H,m), 7.95 (1H,s), 8.03 (1H,s)
9160	$C_{37}H_{36}N_4O_5S$	649(100)	ESI	$CDCl_3$/400MHz	2.72-2.92 (8H,m), 3.09 (3H,s), 3.68 (2H,s), 3.84 (2x3H,s), 6.57 (1H,s), 6.61 (1H,s), 7.06 (1H,d), 7.08 (1H,s) 7.12 (1H,s), 7.22-7.29 (4H,m), 7.38 (1H,m), 7.55-7.59 (4H,m), 7.82 (1H,m), 7.97 (1H,s), 8.04 (1H,s)
9155	$C_{37}H_{36}N_4O_5S$	649(100)	ESI	$CDCl_3$/400MHz	2.72-2.93 (8H,m), 3.19 (3H,s), 3.65 (2H,s), 3.85 (2x3H,s), 6.54 (1H,s), 6.60 (1H,s), 7.04 (1H,m), 7.08-7.10 (2H,m), 7.22-7.29 (3H,m), 7.45 (1H,m), 7.52-7.60 (4H,m), 7.81 (1H,m), 7.95 (2H,s) 8.38 (1H,s)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9178	$C_{41}H_{40}N_4O_5$			$CDCl_3$/400MHz	2.70-2.95 (8H,m), 3.50 (2H,s), 3.70 (2x3H,s), 4.20 (2H,d), 4.65 (1H,d), 4.90 (1H,d), 5.45 (1H,m), 6.45 (1H,s), 6.55 (1H,s), 6.95 (1H,s), 7.10 (2H,d), 7.15 (1H,s), 7.15-7.25 (5H,m), 7.40 (2H,d), 7.55 (2H,d), 7.90 (1H,s), 7.95 (2H,d), (8.85 (1H,s)
9178.HCl	$C_{41}H_{40}N_4O_5$.HCl	669(20)	DCI	$CDCl_3$/400MHz	2.75-3.65 (8H,m), 3.70 (3H,s), 3.75 (2H,s), 3.80 (3H,s), 4.25 (2H,d), 4.70 (1H,d), 5.00 (1H,d), 5.55 (1H,m), 6.45 (1H,s), 6.55 (1H,s), 6.90 (1H,s), 7.10 (2H,d), 7.20-7.50 (8H,m), 7.80 (2H,d), 8.05 (2H,d), 8.50 (1H,s), 8.50 (1H,s), 9.50 (1H,s)
9179	$C_{41}H_{40}N_4O_5$	669(100)	ESI	$CDCl_3$/400MHz	2.70-2.90 (8H,m), 3.60 (2H,s), 3.80 (2x3H,s), 4.30 (2H,d), 4.75 (1H,d), 5.00 (1H,d), 5.50 (1H,m), 6.55 (1H,s), 6.60 (1H,s), 7.05 (1H,s), 7.15 (1H,s), 7.20-7.60 (11H,m), 7.70 (1H,d), 7.80 (1H,s), 7.90 (1H,s), 8.65 (1H,brs)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9193	$C_{43}H_{40}N_4O_5$			$CDCl_3$/400MHz	2.80-2.90 (8H,m), 3.05 (3H,s), 3.68 (2H,s), 3.82 (2x3H,s), 6.55 (1H,s), 6.65 (1H,s), 7.10 (1H,s), 7.28 (2H,d), 7.41 (1H,d), 7.49 (1H,s), 7.51-7.60 (6H,m), 7.78 (2H,d), 7.85 (3H,m), 7.95 (2H,d), 8.05 (1H,s)
9193.HCl	$C_{43}H_{40}N_4O_5$.HCl			d_6-DMSO/400MHz	2.90 (3H,s), 2.95 (2H,bs), 3.10 (4H,m), 3.40 (2H,bs), 3.75 (2x3H,s), 4.25 (1H,s), 4.49 (1H,bs), 6.78 (1H,s), 6.80 (1H,s), 6.91 (1H,s), 7.25 (1H,s), 7.30 (2H,d), 7.50 (1H,dd), 7.53 (2H,m), 7.75 (4H,m), 7.95 (4H,m), 8.02 (2H,d), 10.38 (1H,s), 10.58 (1H,bs), 10.68 (1H,s)
9194.HCl	$C_{43}H_{40}N_4O_5$.HCl	693(100)	ESI	d_6-DMSO/400MHz	2.65 (3H,s), 2.95 (2H,m), 3.12 (4H,m), 3.42 (2H,m), 3.73 (2x3H,s), 4.26 (1H,m), 4.50 (1H,bd), 6.79 (1H,s), 6.82 (1H,s), 6.93 (1H,s), 7.30 (2H,d), 7.48 (1H,d), 7.50 (1H,s), 7.51-7.62 (3H,m), 7.76 (4H,m), 7.90-8.02 (5H,m), 10.30 (1H,s), 10.50 (1H,s), 10.69 (1H,s)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9195	$C_{43}H_{40}N_4O_5$	693	ESI	$CDCl_3$/400MHz	2.74-2.94 (8H,m), 2.80 (3H,s), 3.65 (2H,s), 3.85 (2x3H,s), 6.50 (1H,s), 6.60 (1H,s), 7.12 (1H,s), 7.25 (2H,d), 7.30 (1H,d), 7.48 (1H,t), 7.54 (6H,m), 7.68 (1H,s), 7.80-7.94 (4H,m), 8.0 (2H,s), 8.52 (1H,bs)
9195.HCl	$C_{43}H_{40}N_4O_5$.HCl			d_6-DMSO/400MHz	2.65 (3H,s), 2.94 (2H,m), 3.12 (4H,m), 3.42 (2H,m), 3.73 (2x3H,s), 4.26 (1H,m), 4.50 (1H,bd), 6.79 (1H,s), 6.80 (1H,s), 6.95 (1H,s), 7.30 (2H,d), 7.49 (1H,d), 7.51 (1H,s), 7.52-7.64 (4H,m), 7.78 (2H,d), 7.85-8.00 (5H,m), 8.12 (1H,s), 10.30 (1H,s), 10.50 (1H,s), 10.68 (1H,s)
9196	$C_{37}H_{36}N_4O_6$	633(100)	ESI	$CDCl_3$/400MHz	2.72-2.90 (6H,m), 2.92 (2H,m), 3.4 (3H,s), 3.62 (2H,s), 3.85 (6H,s), 6.52 (1H,m+1H,s), 6.60 (2H,s), 7.08 (2H,d), 7.26 (2H,m), 7.50 (2H,d), 7.54 (3H,m), 7.82 (1H,s), 7.91 (2H,d), 8.00 (1H,s)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9196.HCl	$C_{37}H_{36}N_4O_6$.HCl			d_6-DMSO/400MHz	2.98 (2H,m), 3.12 (4H,m), 3.19 (3H,s), 3.40 (2H,m), 3.75 (2x3H,s), 4.26 (1H,bs), 4.50 (1H,m), 6.68 (1H,m), 6.79 (1H,s), 6.82 (1H,m+1H,s), 6.88 (1H,s), 6.90 (1H,s), 7.30 (2H,d), 7.70 (2H,d), 7.76 (2H,d), 7.87 (1H,d), 8.01 (2H,d), 10.30 (1H,s), 10.55 (1H,bs), 10.60 (1H,s)
9197.HCl	$C_{37}H_{36}N_4O_6$.HCl	633(100)	ESI	d_6-DMSO/400MHz	2.98 (2H,bd), 3.15 (4H,m), 3.21 (3H,s), 3.42 (2H,m), 3.75 (2x3H,s), 4.28 (1H,m), 4.50 (1H,bd), 6.62 (1H,m), 6.78 (1H,s), 6.82 (1H,d), 6.83 (1H,s), 6.89 (2x1H,s), 7.30 (2H,d), 7.56 (1H,t), 7.71-7.78 (3H,m), 7.90 (2H,m), 8.10 (1H,s), 10.30 (1H,s), 10.70 (1H,s), 10.76 (1H,bs)
9198	$C_{38}H_{39}N_5O_5$	646(100)	ESI	d_6-DMSO/400MHz	2.61 (6H,m), 2.81 (2H,t), 3.06 (3H,s), 3.55 (2H,s), 3.65 (3H,s), 3.70 (6H,s), 6.18 (2H,m), 6.65 (2x1H,s), 6.82 (1H,s), 6.98 (1H,s+1H,m), 7.25 (2H,d), 7.68 (4H,m), 7.98 (2H,d), 10.15 (1H,s), 10.50 (1H,s)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9199	$C_{38}H_{37}N_5O_5$	646(100)	ESI	d_6-DMSO/400MHz	2.70 (6H,m). 2.81 (2H,t). 3.06 (3H,s). 3.55 (2H,s). 3.65 (3H,s). 3.70 (6H,s). 3.16 (2H,m). 6.65 (2x1H,s). 6.85 (1H,s). 6.98 (1H,s+1H,m). 7.25 (2H,d). 7.55 (1H,t). 7.68 (2H,d). 6.71 (1H,d). 7.85 (1H,d). 8.10 (1H,s). 10.16 (1H,s). 10.60 (1H,bs)
9209	$C_{43}H_{40}N_4O_5$	693(100)	ESI	d_6-DMSO/400MHz	2.60 (6H,m). 2.80 (2H,t). 3.58 (3H,s). 3.70 (6H,s). 6.62 (1H,s). 6.66 (1H,s). 6.91 (1H,s). 7.36 (3H,m). 7.50 (1H,d). 7.52-7.62 (3H,m). 7.70 (2H,d). 7.76 (1H,d). 7.89 (1H,d). 7.90-799 (4H,m). 8.14 (1H,s). 10.20 (1H,s). 10.73 (1H,s)
9210	$C_{47}H_{41}N_5O_5$	696(100)	ESI	d_6-DMSO/400MHz	2.69 (6H,m). 2.82 (2H,t). 3.06 (3H,s). 3.55 (2H,s). 3.70 (2x3H,s). 3.88 (3H,s). 6.65 (2x1H,s). 6.85 (1H,s). 7.16 (1H,t). 7.20-7.29 (4H,m). 7.50 (1H,d). 7.58 (1H,d). 7.63 (1H,s). 7.70 (2H,d). 7.75 (2H,d). 7.99 (2H,d). 10.14 (1H,s). 10.45 (1H,bs)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9211	$C_{42}H_{40}N_4O_5$	713	ESI	d_6-DMSO/400MHz	2.3 (3H,s), 2.7 (6H,m), 2.82 (2H,t), 2.98 (3H,s), 3.57 (2H,s), 3.7 (2x3H,s), 6.65 (2x1H,s), 6.93 (1H,s), 7.12 (1H,s), 7.26 (2H,d), 7.38-7.48 (2H,m), 7.56 (1H,t), 7.69 (2H,d), 7.78 (1H,d), 7.80 (1H,d), 7.88 (1H,d), 7.95 (1H,d), 8.15 (1H,s), 10.17 (1H,s), 10.79 (1H,bs)
9214	$C_{42}H_{40}N_4O_5$	696(100)	ESI	d_6-DMSO/400MHz	2.63-2.73 (6H,m), 2.81 (2H,t), 3.08 (3H,s), 3.55 (2H,s), 3.71 (2x3H,s), 3.87 (3H,s), 6.65 (2x1H,s), 6.88 (1H,s), 7.18 (1H,t), 7.28 (4H,m), 7.48-7.57 (3H,m), 7.63 (1H,s), 7.69 (2H,d), 7.75 (1H,d), 7.85 (1H,d), 8.12 (1H,s), 10.20 (1H,s), 10.54 (1H,s)
9215	$C_{42}H_{40}N_4O_5S$	713(100)	ESI	d_6-DMSO/400MHz	2.30 (3H,s), 2.70 (6H,m), 2.80 (2H,t), 2.98 (3H,s), 3.55 (2H,s), 3.71 (6H,s), 6.63 (2x1H,s), 6.89 (1H,s), 7.12 (1H,s), 7.24 (2H,d), 7.35-7.45 (2H,m), 7.65 (2H,d), 7.79 (3H,m), 7.97 (1H,d), 8.00 (2H,d), 10.15 (1H,s), 10.72 (1H,bs)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9217	$C_{41}H_{40}N_4O_7$	701(100)	CI	$CDCl_3$/400MHz	2.70-2.95 (8H,m), 3.65 (3H,s), 3.70 (2H,s), 3.80 (2x3H,s), 4.30 (2H,s), 6.50 (1H,s), 6.60 (1H,s), 7.10 (1H,s), 7.20-7.55 (13H,m), 7.85 (1H,s), 7.90 (1H,s), 8.10 (1H,s)
9228	$C_{36}H_{40}N_4O_5$	609(100)	ESI	d_6-DMSO/400MHz	1.08 (6H,d), 2.69 (6H,m), 2.80 (2H,t), 2.88-2.99 (1H,m), 3.34 (3H,s), 3.55 (2H,s), 3.70 (6H,s), 5.84 (1H,d), 6.62 (2x1H,s), 6.78 (1H,s), 7.23 (2H,d), 7.68 (4H,m), 7.98 (2H,d), 10.18 (1H,s), 10.41 (1H,bs)
9229	$C_{35}H_{44}N_4O_5$	649(100)	ESI	d_6-DMSO/400MHz	1.10-1.38 (5H,m), 1.60-1.73 (5H,m), 2.50-2.63 (1H,m), 2.63-2.73 (6H,m), 2.76-2.83 (2H,t), 3.32 (3H,s), 3.55 (2H,s), 3.70 (2x3H,s), 5.86 (1H,d), 6.62 (2x1H,s), 6.80 (1H,s), 7.23 (2H,d), 7.67 (4H,m), 7.97 (2H,d), 10.15 (1H,s), 10.39 (1H,bs)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9230	$C_{39}H_{44}N_4O_5$	649(100)	ESI	$CDCl_3$/400MHz	1.03-1.35 (5H,m), 1.60-1.80 (5H,m), 2.49-2.60 (1H,m), 2.70-2.94 (8H,m), 3.35 (3H,s), 3.63 (2H,s), 3.83 (2x3H,s), 5.93 (1H,d), 6.55 (1H,s), 6.60 (1H,s),7.02 (1H,s), 7.20 (2H,d), 7.50-7.60 (4H,m), 7.86 (1H,m), 7.92 (1H,s), 8.50 (1H,s), 8.98 (1H,bs)
9231	$C_{37}H_{42}N_4O_5$	623(100)	ESI	$CDCl_3$/400MHz	0.92 (3H,t), 1.40 (2H,m), 1.52 (2H,m), 2.43 and 2.76 (2H, two quartets) 2.71-2.92 (8H,m), 3.31 and 3.46 (3H, two singlets), 3.68 (2H,s), 3.85 (6H,s), 5.75 and 6.30 (1H,t), 6.55 (1H,s), 6.60 (1H,s), 7.00 1H, two singlets), 7.28 (2H,d), 7.50 (2H,d), 7.60 (2H,d), 7.80 (1H,s), 7.85 (1H,bs), 7.93 (2H,d)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9232	$C_{37}H_{52}N_4O_5$	623	ESI	$CDCl_3$/400MHZ	0.90 (3H,t), 1.29-1.50 (4H,m), 2.36 and 2.68 (2H, two quartets), 2.72-2.94 (8H,m), 3.27 and 3.36 (3H, two singlets), 3.65 (2H,s), 3.83 (2x3H,s), 5.68 and 6.12 (1H, two triplets), 6.56 (1H,s), 6.60 (1H,s), 6.98 and 6.90 (1H, two singlets),7.20 (2H,m), 7.52 (2H,d), 7.58 (2H,m), 7.85 (1H,m), 7.94 (1H,m), 8.35 and 8.40 (1H, two singlets), 8.58 and 8.83 (1H, two broad singlets)
9233	$C_{36}H_{40}N_4O_5$	609(100)	ESI	$CDCl_3$/400MHz	1.08 (6H,d), 2.71-2.92 (9H,m), 3.35 (3H,s), 3.65 (2H,s), 3.83 (2x3H,s), 5.93 (1H,d), 6.55 (1H,s), 6.60 (1H,s), 7.02 (1H,s), 7.22 (2H,d), 7.54 (4H,m), 7.82 (1H,m), 7.81 (1H,s), 8.37 (1H,s), 8.82 (1H,bs)
9234	$C_{38}H_{44}N_4O_5$	637(100)	ESI	$CDCl_3$/400MHz	1.01 (9H,s), 2.38 (2H,d), 2.74-2.98 (8H,m), 3.47 (3H,s), 3.67 (2H,s), 3.84 (2x3H,s), 6.42 (1H,t), 6.55 (1H,s), 6.62 (1H,s), 7.28 (2H,d), 7.52 (2H,d), 7.58 (2H,d), 7.75 (1H,s), 7.82 (1H,s), 7.92 (2H,d)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9235	$C_{39}H_{44}N_4O_5$	637(100)	ESI	$CDCl_3$/400MHz	0.99 (9H,s), 2.31 and 2.70 (2H, two doublets), 2.71-2.92 (8H,m), 3.32 and 3.40 (3H, two singlets), 3.65 (2H,s), 3.85 (2x3H,s), 5.79 and 6.32 (1H, two triplets), 6.54 (1H,s), 6.60 (1H,s), 7.02 (1H, two singlets), 7.25 (2H,m), 7.56 (4H,m), 7.80 (1H,m), 7.88 (1H, two singlets), 7.96 (1H,s), 8.05 (1H,bs), 8.22 (1H,bs)
9236	$C_{42}H_{46}N_4O_5$	687(100)	ESI	d_6-DMSO/400MHz	1.50 (1H,m), 1.73 (3H,s), 1.83-1.84 (1H,m), 2.10 (1H,m), 2.19 (3H,m), 2.30 (1H,m), 2.70 (6H,m), 2.80 (2H,m), 3.08 (3H,s), 3.55 (2H,s), 3.70 (6H,s), 4.72 (2H,s), 5.67 (1H,bs), 6.39 (1H,bs), 6.62 (2x1H,s), 6.80 (1H, two singlets), 7.23 (2H,d), 7.68 (4H,d), 8.00 (2H,d), 10.18 (1H,s), 10.55 (1H,bs)
9241	$C_{40}H_{38}N_4O_7$	687(100)	ESI	$CDCl_3$/400MHz	2.65-2.90 (8H,m), 3.55 (2H,s), 3.70 (2x3H,s), 4.00 (2H,s), 6.60 (1H,s), 6.65 (1H,s), 6.85 (1H,s), 7.10 (1H,s), 7.25 (2H,d), 7.35-7.45 (6H,m), 7.55 (1H,t), 7.65 (2H,d), 7.70 (1H,d), 7.85 (1H,d), 8.10 (1H,s), 10.10 (1H,s), 10.70 (1H,brs)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9250	$C_{42}H_{46}N_4O_5$	687(100)	ESI	d_6-DMSO/400MHz	1.50-1.60 (1H,m), 1.73 (3H,s), 1.82 (1H,m), 2.1 (1H,m), 2.2 (3H,m), 2.31 (1H,m), 2.71 (6H,m), 2.81 (2H,t), 3.10 (3H,s), 3.56 (2H,s), 3.70 (2x3H,S), 4.75 (2H,s), 5.68 (1H,bs), 6.38 (1H,s), 6.65 (2x1H,s), 6.85 (1H, two singlets) 7.25 (2H,d), 7.54 (1H,t), 7.70 (3H,m), 7.85 (1H,d), 8.07 (1H,s), 10.18 (1H,s), 10.55 (1H,s).
9260	$C_{37}H_{36}N_4O_5$	617(100)	CI	$CDCl_3$/400MHz	2.70-2.80 (6H,m), 3.05 (3H,s), 3.60 (2H,s), 3.65 (2H,m), 3.75 (2x3H,s), 6.50 (1H,s), 6.60 (1H,s), 7.0-8.1 (15H,m)
9261	$C_{37}H_{35}N_4O_5$	617(100),615(60)	CI	$CDCl_3$/400MHz	2.80 (6H,m), 3.05 (3H,s), 3.60 (2H,s), 3.65 (2H,m), 3.80 (2x3H,s), 6.50 (1H,s), 6.52 (1H,s), 7.0-8.10 (15H,m)
9266	$C_{35}H_{38}N_4O_5$	595	CI	$CDCl_3$/400MHz	2.80 (8H,m), 3.10 (2H,q), 3.20 (3H,s), 3.60 (2H,s), 3.65 (2H,t), 3.80 (2x3H,s), 5.70 (1H,t), 6.50 (1H,s), 6.60 (1H,s), 6.80 (1H,brs), 6.95 (1H,s), 7.15-7.90 (10H,m)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9267	$C_{35}H_{38}N_4O_5$	595	CI	$CDCl_3$/400MHz	2.80 (8H,m), 3.10 (2H,q), 3.20 (3H,s), 3.65 (2H,s), 3.70 (2H,t), 3.80 (2x3H,s), 5.70 (1H,t), 6.52 (1H,s), 6.60 (1H,s), 6.95 (1H,s), 7.0 (1H,brs), 7.10-8.10 (9H,m)
9272	$C_{41}H_{40}N_4O_7$	190(100)	CI	$CDCl_3$/400MHz	2.30 (3H,s), 2.70-2.90 (8H,m), 3.00 (3H,s) 3.65 (2H,s), 3.80 (2x3H,s), 6.58 (1H,s), 6.65 (1H,s), 7.05 (1H,s), 7.10 (2H,d), 7.20-7.30 (5H,m), 7.50-7.60 (4H,m), 7.80 (1H,d), 8.00 (1H,s), 8.10 (1H,s), 8.70 (1H,brs)
9273				$CDCl_3$/400MHz	2.30 (3H,s), 2.70-2.90 (8H,m), 3.00 (3H,s), 3.60 (2H,s), 3.80 (2x3H,s), 6.55 (1H,s), 6.60 (1H,s), 7.00 (1H,s), 7.00-7.60 (10H,m), 7.85 (2H,t), 8.05 (1H,s), 8.10 (1H,s), 8.75 (1H,brs)
9274				$CDCl_3$/400MHz	2.25 (3H,s), 2.70-2.90 (8H,m), 3.0 (3H,s), 3.65 (2H,s), 3.85 (2x3H,s), 6.55 (1H,s), 6.60 (1H,s), 7.05 (1H,s), 7.10 (1H,s), 7.10-7.60 (11H,m), 7.80 (1H,d), 8.00 (1H,s), 8.45 (12H,brs)

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9275	$C_{42}H_{45}N_5O_5$	700(100)	ESI	$CDCl_3$/400MHz	2.00 (6H,s), 2.20 (2H,t), 2.75-2.95 (8H,m), 3.65 (2H,s), 3.75 (2H,t), 3.85 (2x3H,s), 6.55 (1H,s), 6.60 (1H,s), 7.05 (1H,s), 7.20 (1H,s), 7.20-7.60 (10H,m), 7.90 (1H,d), 7.95 (1H,s), 8.00 (1H,s), 8.20 (1h,brs)
9276	$C_{39}H_{38}N_4O_6$	659(100)	CI	$CDCl_3$/400MHz	2.75-2.95 (8H,m), 3.00 (3H,s), 3.70 (2H,s), 3.90 (2x3H,s), 6.55 (1H,s), 6.65 (1H,s), 6.80 (2H,d), 7.00-7.30 (6H,m), 7.60 (4H,m), 7.80 (1H,d), 8.00 (1H,s), 8.40 (1H,s), 8.60 (1H,s)
9299	$C_{42}H_{42}N_4O_7$	715(50)	ESI	$CDCl_3$/400MHz	1.20 (3H,t), 2.70-2.90 (8H,m), 3.65 (2H,s), 3.80 (2x3H,s), 3.90 (2H,q), 4.30 (2H,s), 6.55 (1H,s), 6.60 (1H,s), 7.05 (1H,s), 7.20-7.45 (9H,m), 7.55 (4H,m), 8.00 (1H,s), 8.05 (1H,s), 8.45 (1H,brs)
9300				d_6-DMSO/400MHz	2.65-2.85 (8H,m), 2.85 (3H,s), 3.55 (2H,s), 3.70 (2x3H,s), 6.65 (2x1H,s), 6.85 (3H,m), 7.05 (1H,s), 7.10-7.75 (8H,m), 7.85 (1H,d), 8.10 (1H,s), 9.75 (1H,s), 10.15 (1H,s), 10.60 (1H,brs)

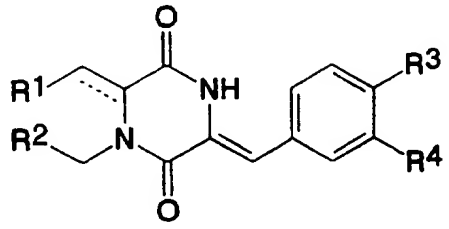
No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
9300.HCl				d_6-DMSO/400MHz	2.85 (3H,s), 2.90-3.30 (8H,m), 3.35 (2H,s), 3.70 (2x3H,s), 6.80-6.95 (5H,m), 7.05 (1H,s), 7.10-7.35 (6H,m), 7.60 (1H,t), 7.75 (2H,m), 7.85 (1H,d), 8.10 (1H,s), 9.90 (1H,s), 10.25 (1H,s)
9301				$CDCl_3$/400MHz	2.70-2.85 (8H,m), 2.90 (3H,s), 3.50 (2H,s), 3.65 (2x3H,s), 6.65 (2x1H,s), 6.70-6.80 (3H,m), 6.85 (1H,s), 7.00 (1H,s), 7.20-7.85 (9H,m), 8.10 (1H,s), 9.50 (1H,s), 10.20 (1H,s)
9306.HCl	$C_{37}H_{42}N_4O_5$.HCl			d_6-DMSO/400MHz	0.90 (3H,t), 1.30-1.52 (4H,m), 2.68 (2H,q), 2.90-3.00 (2H,m), 3.10 (4H,m), 3.20 (3H,s), 3.30 (2H,m), 3.75 (2x3H,s), 4.25 (1H,dd), 4.50 (1H,bd), 5.75 (1H,t), 6.78 (1H,s), 6.81 (1H,s), 6.83 (1H,s), 7.30 (2H,d), 7.52 (1H,t), 7.69 (1H,d), 7.78 (2H,d), 7.85 (1H,d), 8.06 (1H,s), 10.30 (1H,s), 10.42 (1H,s), 10.56 (1H,bs)
9308	$C_{39}H_{38}N_4O_5$	645	Cl	$CDCl_3$/400MHz	2.60-2.95 (8H,m), 3.15 (3H,s), 3.20 (2H,d), 3.70 (2H,d), 3.70 (2H,s), 3.85 (2x3H,s), 4.30 (1H,t), 6.55 (1H,s), 6.60 (1H,s), 6.65 (1H,s), 7.05-8.50 (15H,m)

TABLE 10

No.	Mol. Formula	mass spec data		^{1}H nmr data	
		mass (intensity)	mode	solvent/field	δ
4.1				$CDCl_3$/400MHz	2.70-2.94 (8H,m), 3.64 (2H,s), 3.83 (2x3H,s), 6.53 (1H,s), 6.60 (1H,s), 7.27 (2H,d), 7.57 (2H,d), 7.68 (1H,t), 7.93 (1H,s), 8.03 (1H,d), 8.19 (1H,d), 8.34 (1H,s), 10.09 (1H,s)
4.2				$CDCl_3$/400MHz	2.72-2.96 (8H,m), 3.65 (2H,s), 3.82 (2x3H,s), 6.54 (1H,s), 6.61 (1H,s), 7.28 (2H,d), 7.56 (2H,d), 7.82 (1H,s), 7.97-8.04 (4H,m), 10.11 (1H,s)
4.3	$C_{26}H_{26}N_2O_4$	431(80)	CI	$CDCl_3$/400MHz	2.92 (4H,m), 3.70(2H,s), 3.82-3.87 (8H,m), 6.50 (1H,s), 6.61 (1H,s), 7.47 (2H,d), 7.64 (2H,d), 7.70 (1H,t), 7.97 (1H,s), 8.05 (1H,m), 8.37 (1H,m), 10.12 (1H,s)
4.4	$C_{28}H_{30}N_2O_4$	459(100), 445(60)	CI	$CDCl_3$/400MHz	1.93 (2H,m), 2.47-2.85 (8H,m), 3.57 (2H,s), 3.83 (2x3H,s), 6.53 (1H,s), 6.60 (1H,s), 7.24 (2H,d), 7.59 (2H,d), 7.68 (1H,m), 8.04 (2H,m), 8.20 (1H,m), 8.37 (1H,s), 10.09 (1H,s)
4.5	$C_{26}H_{26}N_2O_4$	431(3), 192(100)	CI	$CDCl_3$/400MHz	2.86-3.04 (4H,m), 3.72 (2H,s), 3.84 (2x3H,s), 3.88 (2H,s), 6.48 (1H,s), 6.61 (1H,s), 7.40-8.10 (8H,m), 10.11 (1H,s)
4.6	$C_{25}H_{24}N_2O_2$	385(10), 146(70) 130(100)	CI	$CDCl_3$/400MHz	2.76-3.04 (8H,m), 3.79 (2H,s), 7.00-8.10 (13H,m), 10.10 (1H,s)

CLAIMS

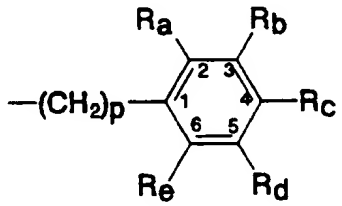
1. A piperazinedione derivative of the formula (I):



(I)

wherein

R_1 is (i) a group



wherein p is 0 or 2;

each of Ra to Re, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_2-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nCO_2R^{11}$;

wherein n is 0 or is an integer of from 1 to 6, each of R^{11}

and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of Ra and Rb, Rb and Rc, Rc and Rd or Rd and Re together form a methylenedioxy group, or form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted;

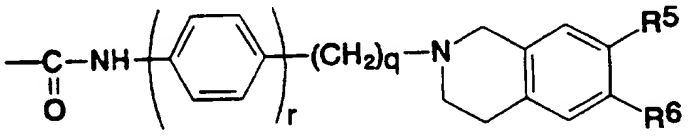
(ii) a 5- or 6-membered heterocyclic group containing at least one heteroatom selected from O, N and S, which group may be fused to a benzene ring;

(iii) a C_1-C_6 alkyl or C_5-C_7 cycloalkyl group; or

(iv) a C_5-C_7 cycloalkenyl group which is unsubstituted or substituted by C_2-C_6 alkenyl;

R^2 is H, C_1-C_6 alkyl optionally substituted by a group $-N(R^{11}R^{12})$ as defined above, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, $-COOR^{11}$ wherein R^{11} is as defined above or a phenyl group as defined under (i) above, but is other than H when R^1 is unsubstituted phenyl;

one of R^3 and R^4 is hydrogen and the other is a group of formula (A):



(A)

wherein q is an integer of 1 to 4, r is 0 or 1 and R^5 and R^6, which may be the same or different, are each H or C_1-C_6 alkoxy, or R^5 and R^6 together form a methylenedioxy group; and ------ is a double bond or, when R_1 is as defined under (i) above, is a double bond or a single bond;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is a phenyl group as defined under (i) in which one of Ra to Re is selected from hydroxy, C_1-C_6 alkoxy, $NHCOR^{11}$, $-CO_2R^{11}$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, NO_2, $-SO_2N(R^{11}R^{12})$, $-SOR^{13}$, $-N(R^{11})COR^{12}$ and halogen, and the other four of Ra to Re are H.

3. A compound according to claim 1 or 2 wherein R^1 is a phenyl group as defined under (i) in which each of Ra to Re is hydrogen, or one of Ra, Rb and Rc is halogen or C_1-C_6 alkoxy and the rest of Ra to Re are hydrogen; or is a pyridyl, furyl or thienyl group;
R^2 is H, CH_3, cyclopropyl or phenyl; and
one of R^3 and R^4 is H and the other is a group of formula (A) wherein q is 2 and each of R^5 and R^6 is a methoxy group.

4. A compound according to claim 1, 2 or 3 wherein R^1 is a 4-pyridyl, 3-furyl, 2-thienyl or 3-thienyl group.

5. A compound selected from:

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-ethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9112)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-benzyl-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9113)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-benzylidene-1-cyclopropylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9114)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(3-furylmethylene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9108)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(4-methoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9109)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(4-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9091)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(2-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9092)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(3-

chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide, hydrochloride (9093)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-pyridylmethylene)-3-piperazinylidene)methylbenzamide, hydrochloride (9110)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-thenylidene)-3-piperazinylidene)methylbenzamide, hydrochloride (9111)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-2,5-dioxo-6-(2-thenylidene)-3-piperazinylidene)methylbenzamide (9155)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-thenylidene)-3-piperazinylidene)methylbenzamide (9160)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9157)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-

isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(2-chlorobenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9158)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-furylmethylene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9159)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-methoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9156)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-ethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9139)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-cyclopropylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9141)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-allyl-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9178)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-allyl-6-benzylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9179)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9193)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(1-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9194)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(1-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9195)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(2-furyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9196)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-

3-((3Z,6Z)-6-(2-furyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9197)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(1-methyl-3-pyrrolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9198)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(1-methyl-3-pyrrolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9199)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9209)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(1-methyl-3-indolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9210)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(3-methylbenzo(b)thien-2-yl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9211)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(1-methyl-3-indolyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9214)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(3-methylbenzo(b)thien-2-yl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9215)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-methoxycarbonylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9217)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-(2-methylpropylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide (9228)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-6-cyclohexylmethylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9229)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-

3-((3Z,6Z)-1-methyl-6-cyclohexylmethylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9230)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-pentylidene-3-piperazinylidene)methylbenzamide (9231)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)--3-((3Z,6Z)-1-methyl-2,5-dioxo-6-pentylidene-3-piperazinylidene)methylbenzamide (9232)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-1-methyl-6-(2-methylpropylidene)-2,5-dioxo-3-piperazinylidene)methylbenzamide (9233)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-(3,3-dimethylbutylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9234)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3,3-dimethylbutylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9235)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-4-((3Z,6Z)-6-((4S)-4-isopropenyl-1-cyclohexenyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9236)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-carboxymethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9241)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-((4S)-4-isopropenyl-1-cyclohexenyl)methylene-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9250)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-3-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9260)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-1-methyl-6-(2-naphthyl)methylene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9261)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-3-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-phenylpropylidene)-3-piperazinylidene)methylbenzamide (9266)

N-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)-4-((3Z,6Z)-1-methyl-2,5-dioxo-6-(3-phenylpropylidene)-3-piperazinylidene)methylbenzamide (9267)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(4-acetoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9272)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-acetoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9273)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(2-acetoxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9274)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-(2-dimethylaminoethyl)-2,5-dioxo-3-piperazinylidene)methylbenzamide (9275)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(4-hydroxybenzylidene)-1-methyl-2,5-dioxo-3-

piperazinylidene)methylbenzamide (9276)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-benzylidene-1-ethoxycarbonylmethyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9299)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(2-hydroxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9300)

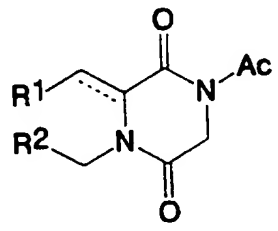
N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6Z)-6-(3-hydroxybenzylidene)-1-methyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9301)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z,6E)-1-methyl-6-pentylidene-2,5-dioxo-3-piperazinylidene)methylbenzamide (9306)

N-(4-(2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)ethyl)phenyl)-3-((3Z)-1-methyl-6-benzyl-2,5-dioxo-3-piperazinylidene)methylbenzamide (9308)

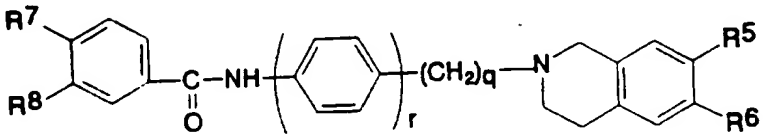
6. A pharmaceutical or veterinary composition comprising a pharmaceutically acceptable carrier or diluent and, as an active principle, a compound as claimed in any one of the preceding claims.

7. A process for producing a compound as defined in claim 1, which process comprises treating a compound of formula (II)



(II)

wherein R^1, R^2 and ----- are as defined in claim 1, with a compound of formula (III):



(III)

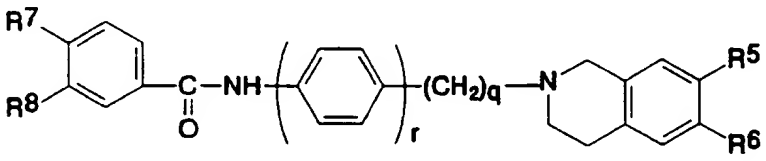
wherein one of R^7 and R^8 is hydrogen and the other is -CHO, and q, r, R^5 and R^6 are as defined in claim 1; in the presence of a base in an organic solvent; and, if desired, converting the resulting compound into a pharmaceutically acceptable salt thereof.

8. A compound as defined in any of claims 1 to 5 for use as a modulator of multi-drug resistance.

9. Use of a compound as defined in any one of claims

1 to 5 in the manufacture of a medicament for use as a modulator of multi-drug resistance.

10. A compound of formula III:



(III)

wherein q, r, R^5 and R^6 are as defined in claim 1, one of R^7 and R^8 is hydrogen and the other of R^7 and R^8 is -CHO.